9. QUANTITATIVE RISK ASSESSMENT FOR 1,3-BUTADIENE

9.1. EPIDEMIOLOGICALLY BASED CANCER RISK ASSESSMENT

9.1.1. Exposure-Response Modeling

In general, it is preferable to use high-quality epidemiologic data when they are available over toxicologic data for quantitative risk assessment purposes. In the past, available epidemiologic data on 1,3-butadiene have been inadequate for quantitative risk assessment, and previous risk assessments relied primarily on models based on the NTP mouse bioassay studies (reviewed in Chapter 1).

The recently reported findings by Delzell et al. (1995) from a retrospective cohort mortality study of synthetic production workers exposed to 1,3-butadiene (reviewed in Chapter 7) present an opportunity to perform a quantitative risk assessment based on human data. The investigators developed a job exposure matrix (JEM) for 1,3-butadiene, styrene, and benzene based on industrial hygiene data, which contained estimates of the average daily exposure (in ppm based on the 8-h TWA) and the number of annual peaks (defined as $\geq$ 100 ppm for 1,3-butadiene and 50 ppm for styrene) for each area and job code for each study year. The investigators were then able to estimate cumulative exposures (ppm*years and peak*years) by linking the JEM with the study subject's work histories.

Delzell et al. (1995) investigated the relationship between cumulative exposure to 1,3-butadiene and leukemia mortality using Poisson regression analysis (Frome and Checkoway, 1985). The models controlled for the potentially confounding effects of age (40-49, 50-59, 60-69, 70-79, 80+), years since hire (10-19, 20-29, 30+), calendar period (1950-59, 1960-69, 1970-79, 1980-89, 1990-91), and race (black, other). Plant was considered as a possible confounder but was dropped from the final models because it did not affect the estimated parameters for 1,3-butadiene or styrene. Few subjects were exposed to benzene, and benzene did not appear to confound the relationship between 1,3-butadiene or styrene exposure and leukemia mortality. Hence, the model results presented in the report did not control for benzene exposure.

Different functional forms of the relationship between the relative rate (RR) and measures of exposure were evaluated by Delzell et al. (1995) including the following:

(1) Multiplicative: $RR = e^{\beta X}$

(2) Power: $RR = e^{\beta[\ln(1+X)]}$

(3) Linear Excess: $RR = 1 + \beta X$

(4) Polynomial Excess: $RR = 1 + \beta_1 X^p + \beta_2 X^q + ...$

where X represents the 1,3-butadiene or styrene exposure categories using the midpoints of the intervals, β represents the estimated model parameters, and the powers "p" and "q" are fixed real numbers. Although many polynomial functions (model 4) were considered, only the results from a square root model were presented because this was considered to provide the best fit. This model may be represented as:

(5) Square Root: $RR = 1 + \beta_1 X^{½}$

The Poisson regression analyses revealed a positive exposure-response relationship between cumulative exposure to 1,3-Butadiene or styrene and leukemia mortality. This relationship was evident both in models that represented these exposures as categorical variables (see Table 59 in Delzell et al., 1995) and in models where exposure was represented using continuous variables as described above. 1,3-Butadiene and styrene exposures among exposed study subjects were found to be moderately correlated (Spearman's rank correlation, r=0.53). The relationship between 1,3-butadiene cumulative exposure and leukemia mortality appeared to be independent of the styrene exposure and was not appreciably altered by inclusion of styrene cumulative exposure in the model. On the other hand, the relationship between styrene cumulative exposure and leukemia mortality was weakened and irregular when 1,3-butadiene cumulative exposure was controlled for. These findings suggest that 1,3-butadiene cumulative exposure is a more likely explanation for the leukemia excess observed in this cohort than styrene cumulative exposure.

Analyses of peak years indicated an association between this variable and leukemia mortality even after controlling for cumulative exposure, but this relationship was irregular in the categorical regression analyses. Excluding exposures that occurred within 5 or 10 years of death (i.e., lagging exposures) only slightly increased the exposure-response relationship for 1,3-butadiene cumulative exposure; whereas excluding exposures within 20 years of death weakened and almost eliminated the relationship (i.e., see Table 63 in Delzell et al., 1995).

The results that were obtained by the investigators from fitting the alternative relative rate models described above are summarized in Table 9-1. These results are from models that simultaneously evaluated the effects of 1,3-butadiene and styrene exposure. The regression parameter for 1,3-butadiene cumulative exposure was found to be statistically significantly greater than 0 ($p<0.05$) in all of the models evaluated, whereas a nonsignificant and weaker relationship was observed for styrene.

The power and square root models were found to provide the best fit to the data based on comparison of the model deviances. However, the differences in deviances between the various

Table 9-1. Results from exposure-response models of continuous cumulative exposure to 1,3-butadiene and styrene using alternative structural forms reported by Delzell et al. [a]

Structural model form	1,3-Butadiene (ppm-years)			Styrene (ppm-years)		
	Model deviance	β estimate (S.E.) [b]	LRT p-value [c]	Model deviance	β Estimate (S.E.) [b]	LRT p-value [c]
Multiplicative: $RR = e^{\beta X}$	486.0	0.0041 (0.0019)	0.04	485.9	0.0052 (0.0053)	0.34
Linear: $RR = 1 + \beta X$	486.0	0.0068 (0.0050)	0.04	485.7	0.0079 (0.0088)	0.30
Power: $RR = e^{\beta[\ln(1 + X)]}$	485.6	0.2028 (0.0972)	0.03	485.2	0.1494 (0.1183)	0.21
Square root: $RR = 1 + \beta_1 X^{1/2}$	485.6	0.1293 (0.1024)	0.03	485.4	0.0968 (0.1090)	0.23

[a] Adapted from Table 67 in Delzell et al. (1995). Results presented are adjusted for age, calendar year, years since hire, race, and exposure to 1,3-butadiene or styrene.
[b] S.E. is the standard error for the exposure parameter estimates.
[c] LRT, likelihood ratio test for the exposure effect (1,3-butadiene or styrene).

models are slight. The authors expressed a preference for the square root model as the best model based on its goodness of fit and its simplicity. This model was refined into a "final model" by omitting styrene and race because the effect of these variables on the estimated parameter for 1,3-butadiene exposure was considered to have been minimal. In addition, certain age, calendar year, and years since hire categories were collapsed for the final model for similar reasons. The final model is summarized in Table 9-2. The relationship between cumulative 1,3-butadiene exposure and leukemia mortality was highly statistically significant in this model (p=0.002).

9.1.2. Prediction of Lifetime Excess Risk of Leukemia

The relative rate models presented in the report by Delzell et al., which are summarized in Tables 9-1 and 9-2, were used as a basis for predicting the lifetime excess risk of leukemia mortality for varying levels of continuous environmental exposures to 1,3-butadiene. These lifetime risk estimates were made using the relative rate estimates and an actuarial program that

Table 9-2. Results from "final" square root exposure-response model of continuous cumulative exposure to 1,3-butadiene reported by Delzell et al. [a]

Variable	βeta		Likelihood ratio test	
	Estimate	S.E. [b]	χ^2 (d.f.) [c]	p-value
Loglinear terms				
Constant	-10.02	0.47		
Age:			13.2 (2)	0.001
40-69	0			
70-79	0.89	0.33		
80+	1.71	0.48		
Calendar year:			3.85(1)	0.050
1950-89	0			
1990-91	0.72	0.34		
Years since hire:			7.64 (1)	0.006
10-19	0			
20+	1.09	0.44		
Linear term				
(1,3-butadiene ppm-years)$^{0.5}$	0.17	0.10	9.41 (1)	0.002

[a] This table is an adaptation of Table 68 in Delzell et al. (1995).
[b] S.E. is the standard error of the parameter estimate.
[c] Chi-square (χ^2) and degrees of freedom (d.f.) based on the likelihood ratio statistic.

takes into account the effects of competing causes of death.[1] U.S. age-specific mortality rates for all race and gender groups combined (NCHS, 1993) were used to specify the leukemia and all-cause background rates in the actuarial program. Exposures to 1,3-butadiene were assumed to be continuous for the entire lifetime, and the risks were computed up to age 85. The occupational 1,3-butadiene exposures in the epidemiologic study were converted to continuous environmental exposures by multiplying the occupational exposure estimates by a factor to account for differences in the number of days exposed per year (365/240 days) and another

[1]This program is an adaptation of the approach that was previously used in BEIR IV. Health Risks of Radon and Other Internally Deposited Alpha Emitters. National Academy Press, Washington, DC, 1988, pp. 131-134.

factor to account for differences in the amount of air inhaled per day (20/10 m^3). The reported standard errors for the 1,3-butadiene regression coefficients were used to compute the upper 95% confidence limits for the relative rates based on a normal approximation.

Point estimates and one-sided upper 95% confidence limits for lifetime risk of leukemia associated with varying levels of environmental exposure to 1,3-butadiene based on the alternative model forms are illustrated in Figures 9-1 to 9-5. Estimates of risks and exposure levels corresponding to levels of risk of potential regulatory interest are presented in Tables 9-3 and 9-4. These estimates appear to vary by several orders of magnitude depending on the model used. For example, at the 1 in a million risk level, the 95% upper confidence intervals for 1,3-butadiene exposure range from 0.1 ppb (parts per billion) (based on the multiplicative model) to 1 e-6 ppb (based on the final square root model).

Consistent with the proposed EPA cancer guidelines, these results were also used to estimate the exposure level (EC_p; "effective concentration") and 95% lower confidence intervals (LEC_p) associated with varying levels of risk (p) ranging from 0.1 to 10%, which are summarized in Table 9-5. Although the new EPA guidelines emphasize the derivation of exposure levels associated with a 10% risk level, this does not seem reasonable in this instance. The 10% level of risk is associated with exposure levels that are higher than most of the exposures experienced by the workers in this epidemiologic study. Furthermore, based on the actuarial program described above, a relative rate of 19 would be required for adults over the age of 20 to increase the lifetime risk of leukemia death by 10%, but the leukemia standardized mortality ratios (SMRs) reported by Delzell et al. (1995) were considerably lower.[2] Hence, these considerations suggest that using a 10% risk level would be an upward extrapolation in this case. A 1% or even a lower (e.g., 0.1%) risk level would seem to be a more reasonable choice in this circumstance. The analogous relative rates for increased risks of 1% or 0.1% are 2.7 and 1.17, respectively, which better correspond with the set of SMRs reported by Delzell et al. (1995). The exposure levels corresponding to a 1% risk level are illustrated in Figures 9-1 to 9-5. When a 1% risk level is used, the LEC_1 from these analyses ranges from 0.07 to 0.6 ppm based on the different relative rate models. Using the final model presented by Delzell et al. (1995) would yield an LEC_1 of 0.12 ppm.

[2]The maximum reported SMR was 13.33. This SMR was based on two leukemia deaths among black men from plant #2 with at least 10 years of work (not all of which was salaried) and at least 20 years of elapsed time since hired. (See Table 29 of Delzell et al., 1995.)

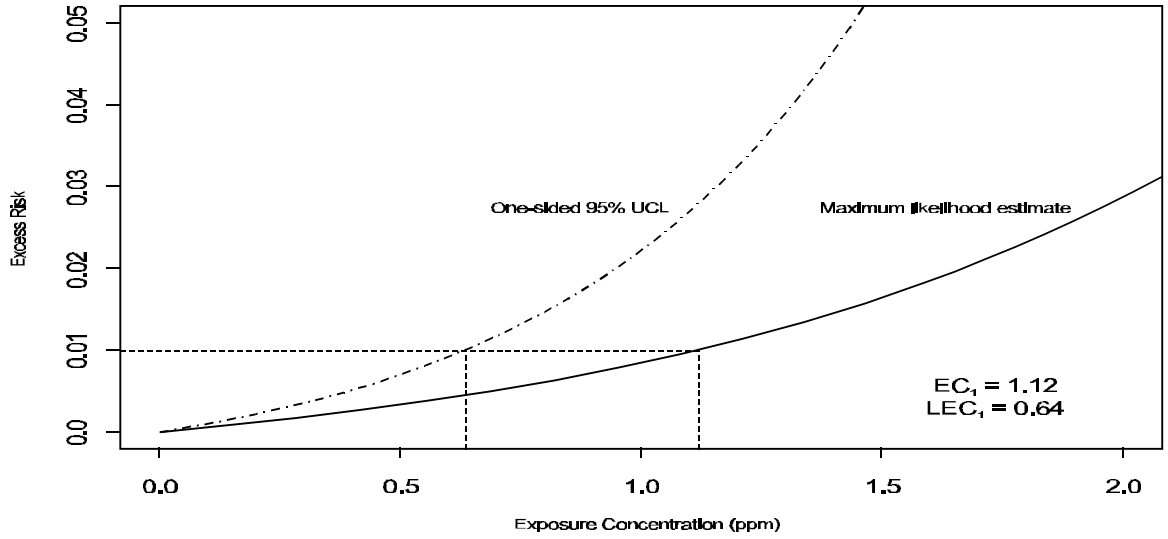
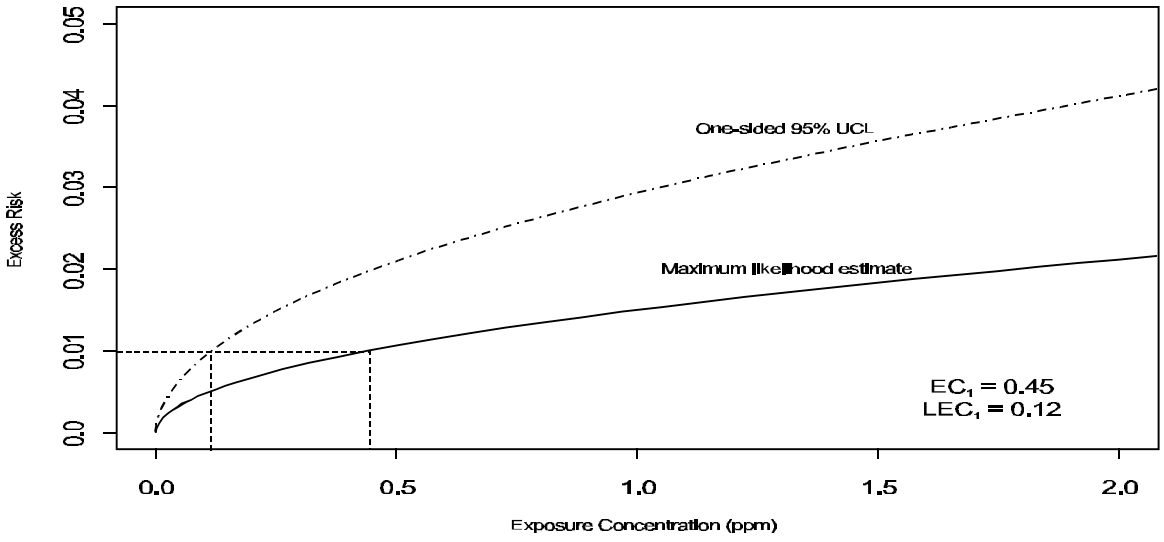


Figure 9-1. Excess risk and 95% upper confidence limit excess risk estimates based on the multiplicative model reported by Delzell et al., 1995.*
* Multiplicative model: $RR = e^{\beta x}$



Figur

e 9-2. Excess risk and 95% upper confidence limit excess risk estimates based on the power model reported by Delzell et al., 1995.*
* Power model: $RR = e^{\beta[1v(1+X)]}$

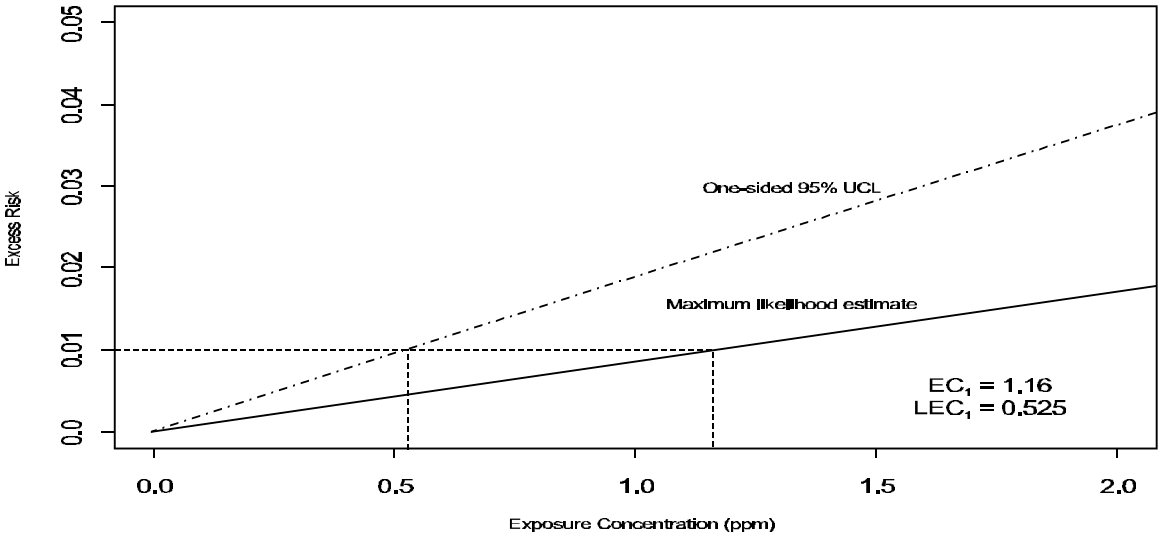


Figure 9-3. Excess risk and 95% upper confidence limit excess risk estimates based on the linear excess relative rate model reported by Delzell et al., 1995.*
* Linear excess model: $RR=1+\beta X$

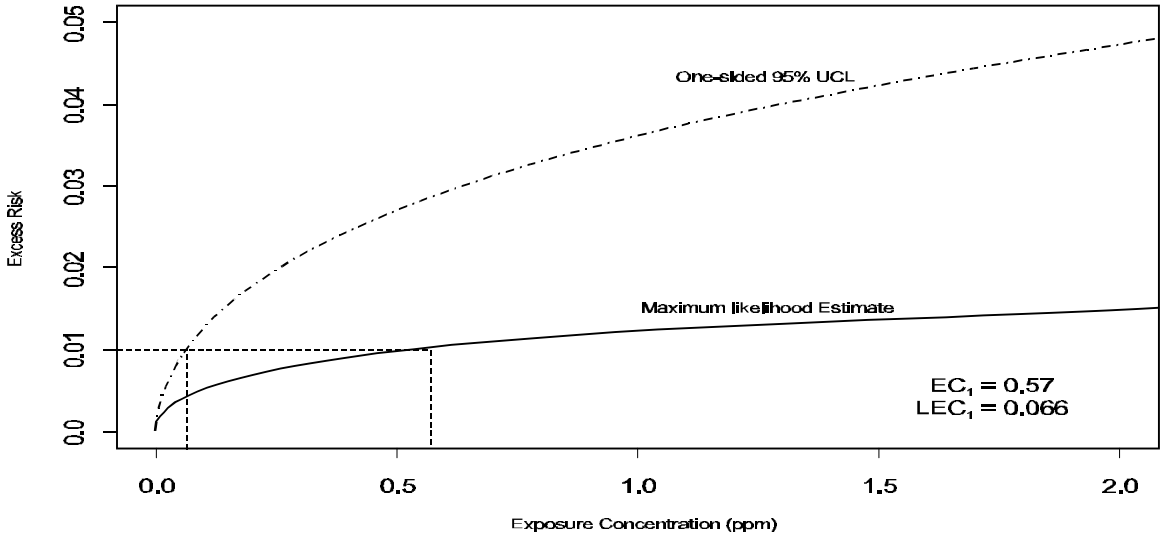


Figure 9-4. Excess risk and 95% upper confidence limit excess risk estimates based on the final square root model reported by Delzell et al., 1995.*
* Final square root model: $RR=1+\beta x^{½}$

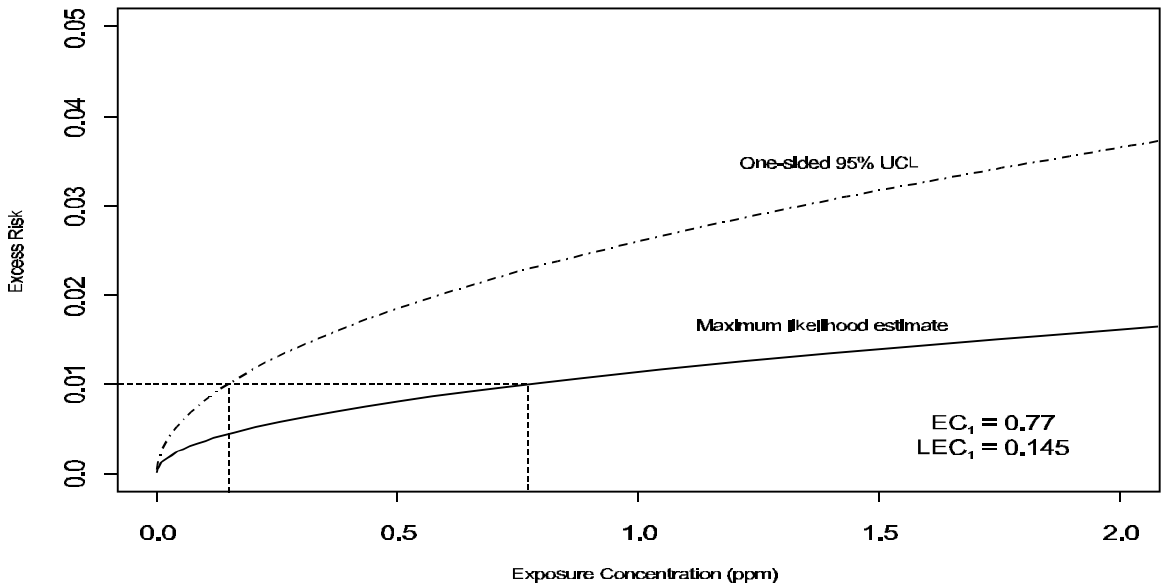


Figure 9-5. Excess risk and 95% upper confidence limit excess risk estimates based on the square root model reported by Delzell et al., 1995.*

* Square root model: $RR=1+\beta x^{1/2}$

Table 9-3. Maximum likelihood estimates (MLEs) of excess risk with one-sided 95% upper confidence limits (95% UCL) from several models reported by Delzell et al. (1995) for continuous lifetime exposures to varying concentrations of 1,3-butadiene

Model	Concentration (ppm)	MLE excess risk	95% UCL excess risk
Multiplicative: $RR = e^{\beta X}$	1.0E-04	5.2E-07	9.2E-07
	1.0E-03	5.2E-06	9.2E-06
	1.0E-02	5.3E-05	9.3E-05
Power: $RR = e^{\beta[\ln(1+X)]}$	1.0E-04	2.6E-05	4.6E-05
	1.0E-03	2.4E-04	4.4E-04
	1.0E-02	1.6E-03	3.1E-03
Linear: $RR = 1 + \beta X$	1.0E-04	8.7E-07	1.9E-06
	1.0E-03	8.7E-06	1.9E-05
	1.0E-02	8.7E-05	1.9E-04
Initial square root: $RR = 1 + \beta_1 X^{1/2}$	1.0E-04	1.1E-04	2.6E-04
	1.0E-03	3.6E-04	8.4E-04
	1.0E-02	1.1E-03	2.6E-03
Final square root: $RR = 1 + \beta_1 X^{1/2}$	1.0E-04	1.5E-04	3.0E-04
	1.0E-03	4.8E-04	9.4E-04
	1.0E-02	1.5E-03	3.0E-03

Ratios are also presented in Table 9-5 that were calculated by dividing the excess risk (p) by the corresponding LEC_p for each model. Each ratio is the slope of the line segment connecting the point (LEC_p, p) with the origin. Based on the LEC_1, these ratios vary by approximately one order of magnitude from 0.016 to 0.15. If these LEC_1-based ratios were used to calculate the concentration corresponding to a 1 in a million excess lifetime risk by linear interpolation[3], the values would range from 7 to 64 parts per trillion. The final model presented by Delzell et al. (1995) would yield a corresponding exposure level of 12 parts per trillion.

Table 9-4. MLEs of parts per million continuous exposure concentrations associated with varying excess risk levels with one-sided 95% lower confidence

[3] Linear interpolation between the origin and the point (LEC_p, p) is also referred to as "linear extrapolation."

limits (95% LCL) based on relative rate results of several models reported by Delzell et al. (1995) and U.S. population rates

Model	Excess risk	MLE (ppm)	95% LCL (ppm)
Multiplicative: $RR = e^{\beta X}$	1E-6	1.9E-4	1.1E-4
	1E-5	1.9E-3	1.1E-3
	1E-4	1.9E-2	1.1E-2
Power: $RR = e^{\beta[\ln(1+X)]}$	1E-6	3.9E-6	2.2E-6
	1E-5	3.9E-5	2.2E-5
	1E-4	4.0E-4	2.2E-4
Linear: $RR = 1 + \beta X$	1E-6	1.1E-4	0.52E-4
	1E-5	1.1E-3	0.52E-3
	1E-4	1.1E-2	0.52E-2
Initial square root: $RR = 1 + \beta_1 X^{1/2}$	1E-6	7.6E-9	1.4E-9
	1E-5	7.6E-7	1.4E-7
	1E-4	7.6E-5	1.4E-5
Final square root: $RR = 1 + \beta_1 X^{1/2}$	1E-6	4.4E-9	1.1E-9
	1E-5	4.4E-7	1.1E-7
	1E-4	4.4E-5	1.1E-5

9.1.3. Sources of Uncertainty

It is apparent from the results presented in Table 9-5 that one major source of uncertainty is the choice of the model for the prediction of risk. The range of values of the LEC at either of the 1% and 10% excess risk levels spanned approximately one order of magnitude, whereas the range for the 0.1% level spanned nearly two orders. In this instance, it seems more reasonable to utilize the results at the 1% risk level because this corresponds to exposures that are within the range of this epidemiologic study. However, it is not possible to clearly choose one of the relative rate models as the best for risk assessment purposes because none of the models has a biologic basis. Furthermore, all the models summarized in Table 9-1 fit the observed data nearly

Table 9-5. Maximum likelihood (EC_p) and 95% lower-bound (LEC_p) estimates of the continuous exposure concentrations associated with varying levels of excess risk (p)

Structural model form	Percentage excess risk (p)	1,3-Butadiene exposure levels (ppm)		Ratio [a]
		Maximum likelihood (EC_p)	Lower 95% bound (LEC_p)	
Multiplicative model: $RR = e^{\beta X}$	10	3.3	1.87	5.3 E-2
	1	1.12	0.64	1.6 E-2
	0.1	0.18	0.10	1.0 E-2
Power: $RR = e^{\beta[\ln(1+X)]}$	10	1000	15	6.7 E-3
	1	0.57	0.066	1.5 E-1
	0.1	0.0054	0.0025	4.0 E-1
Linear model: $RR = 1 + \beta X$	10	12.5	5.65	1.8 E-2
	1	1.16	0.525	1.9 E-2
	0.1	0.116	0.0525	1.9 E-2
Initial square root:	10	88	16.8	5.9 E-3
	1	0.77	0.145	6.9 E-2
	0.1	0.0076	0.00144	6.9 E-1
Final square root: $RR = 1 + \beta_1 X^{1/2}$	10	51	13.5	7.4 E-3
	1	0.45	0.12	8.3 E-2
	0.1	0.0044	0.0012	8.3 E-1

[a] The ratio is the excess risk (p/100%) divided by the one-sided lower 95% confidence limit on the exposure estimate (LEC_p).

as well. Moreover, for a given linear extrapolation, the ratios in Table 9-5 show that the sensitivity of the result to the choice of excess risk level varies considerably for these models, with the linear model being least sensitive and the two square root models being most sensitive. Of the two square root models, however, the final relative rate model could be advantageous to the other model if the omitted parameters for the effects of race and styrene exposure are unnecessary.

A major source of uncertainty in this analysis is the potential for misclassification of exposures in the study by Delzell et al. (1995). This is a frequent limitation of nearly all epidemiologic studies of this type for quantitative risk assessment purposes. The exposures of this study were based on modeling a relatively extensive set of data. However, questions have been raised concerning the accuracy of exposure estimates, particularly for some ill-defined tasks (letter from Elizabeth Moran, CMA, March 25, 1996). For example, the work histories of maintenance laborers do not indicate whether they were vessel cleaners (a high-exposure category) or building cleaners (a low-exposure category). The full impact of this potential for exposure misclassification is unknown, but preliminary analyses suggest that it may have dampened and possibly distorted the observed dose-response relationship (letter from Delzell and Macaluso to Aparna Koppikar, April 2, 1996).

Another concern about the study has been expressed regarding the assignment of peak exposures in the analysis, which was defined as average exposures equal to or greater than 100 ppm over 15 min. It has been suggested that there were tasks with extremely high peak exposures (thousands of ppm) over very short time periods (seconds to a few minutes) (letter from Delzell and Macaluso to Aparna Koppikar, April 2, 1996). The models used in this risk assessment assume a constant dose-rate effect and do not consider the potential for the effects of peak exposures. The potential impact of work area assignments and butadiene peaks on leukemia mortality in this study population is an active area of research among the investigators at the University of Alabama who conducted the study by Delzell et al. (1995).

9.1.4. Summary and Conclusions

Risk estimates for environmental exposures are derived from an analysis by Delzell et al. (1995) of an occupational retrospective cohort mortality study of approximately 16,000 workers in six North American styrene-butadiene rubber manufacturing plants. The analysis of this study is based on follow-up during 1943-1991, with an average follow-up of 25 years and about 25% of the cohort deceased. While overall mortality and all cancer mortality were below expected values based on general population regional rates, the increase in leukemias was statistically significant (SMR = 1.43, 95% C.I. = 1.04-1.91) for all ever-hourly men (Delzell et al., 1996). The consistency of this leukemia result with other findings from previous epidemiology studies with 1,3-butadiene plus other data led to the conclusion that this increase was due to 1,3-butadiene and to the decision to perform a quantitative risk assessment with this database.

While this cohort had been previously studied (Matanoski et al., 1987, 1988, 1989, 1990, 1994), the Delzell et al. update and analyses are especially noteworthy for their extensive work on exposure estimation based on detailed reviews of individual job histories and a job exposure matrix (Delzell et al., 1995; Macaluso et al., 1996). The careful work on exposure allowed

better estimates of risk and dose response. Exposure metrics included cumulative ppm-years and number of years with peak exposures of at least 100 ppm for at least 15 min. Additional individual worker exposure information on both styrene and benzene allowed analyses to adjust for these potential confounding exposures. The Delzell et al. (1995) report includes these analyses.

The Delzell et al. analysis used Poisson regression analysis with nine categories for cumulative exposure of 1,3-butadiene and nine categories of exposure for styrene. The analysis also included, as covariates, adjustments for age, race, calendar year, and years since hire. Relative rate models run within the Poisson analysis included the (1) multiplicative, (2) power, (3) linear, and (4) square root models. The parameter representing cumulative 1,3-butadiene exposure was found to be statistically significant in all the models evaluated, and all models fit the data adequately in the observable range. The cumulative styrene exposure parameter was positive for all the models, but not statistically significant. While Delzell et al. selected the square root model as their final choice because of a slightly better likelihood fit, none of the models fit the data significantly better or worse than the others.

The quantitative risk analysis presented here uses the results of the Delzell et al. analyses, which include the styrene exposure variable as a covariate, to extrapolate risk from occupational work-time exposure to lifetime environmental continuous exposure. This is done by adjusting the 1,3-butadiene parameter estimates calculated by Delzell et al. to reflect continuous rather than work-time exposures and by using life table modeling techniques to convert the relative rate exposure-response relationship to a lifetime additional risk dose-response relationship. These techniques have been used before by EPA as well as other governmental agencies.

After calculation of the exposure-response relationship, the low-exposure extrapolation is done in two ways reflecting the different approaches used in EPA's 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) and those currently proposed for revision (U.S. EPA, 1996). For the 1986 Guidelines, the risk estimates are calculated as a potency or slope factor derived from fitting a linear model (default case) to the observed data and applying the same model to lower exposure concentrations. For the proposed guidelines revisions, the risk estimates are obtained by first calculating a "point of departure" within the range of observation using any of the appropriate models and then extrapolating to 0 by means of a straight line. The LED_{10} (i.e., lower confidence limit on a dose associated with 10% extra risk) is proposed in the guidelines revisions as the standard point of departure; however, the LEC_{01} and EC_{01} are used here because 1% is within the observable range of increased leukemia deaths for the different 1,3-butadiene exposure groups in the Delzell et al. study, because exposure levels are expressed as exposure concentrations rather than doses, and because the issue of whether to use LEDs or EDs in the final guidelines has not yet been resolved.

The results of the extrapolations using the four relative rate models are shown in the quantitative risk analysis and presented in Figures 9-1 to 9-4. They show that although in the observable risk range of 1%, the MLEs of required continuous exposure (EC_{01}) are close, varying 2.6-fold from 0.45 to 1.16 ppm, the LEC_{01} estimates range from 0.066 to 0.64, or about 10-fold. Furthermore, as the risk extrapolation decreases 10-fold to a 0.001 risk level, the ML exposure estimates for the various models diverge much more rapidly, a 45-fold range from 0.004 ppm to 0.18 ppm. At the 10^{-5} risk level, the exposure estimates diverge by nearly four orders of magnitude. Clearly, the final risk estimates based on the 1986 guidelines extrapolation procedures are highly dependent on the choice of model, but those of the proposed guidelines revisions, which extrapolate from the LEC_{01}, are less affected.

For the 1986 guidelines approach, the model of choice is the linear default. This choice is based more on historical precedence and biological plausibility arguments than on statistical fit or conservatism. In fact, for a 10^{-6} risk level the linear model is much less protective of public health, by nearly five orders of magnitude, than is the Delzell et al. square root model choice. For this approach, the maximum likelihood potency (slope) estimate is:

$$B = 8.7 \times 10^{-3} \text{ (ppm)}^{-1}.$$

For the suggested default approach under the proposed guidelines revisions, the EC_{01} level is chosen because that is within the observable response range of leukemia deaths. At the EC_{01} level, the different models provide dose estimates ranging from 0.45 ppm to 1.16 ppm and the 95% LCLs on dose ranging from 0.066 to 0.64. Without specific directions for choice from the proposed guidelines, potency estimates based on each of the models examined by Delzell et al. are presented in Table 9-6.

The cancer potency estimates using EC_{01}s as the point of departure range from 8.7×10^{-3}/ppm (linear model) to 0.022/ppm (final square root model). The square root model was the model preferred by Delzell et al. based on goodness of fit and simplicity; thus they chose that model for various refinements, resulting in the final square root model. The cancer potency estimates based on LEC_{01}s range from 0.016/ppm to 0.15/ppm, with the final square root model yielding 0.083/ppm while the linear model yields 0.019/ppm. Although the proposed Guidelines do not offer explicit guidance on choice of model, it may be appropriate in this particular case to use the final square root model to obtain the point of departure because this model benefits from the refinements performed by Delzell et al.

Table 9-6. Cancer potency (unit risk) estimates based on linear extrapolation from the LEC_{01} or EC_{01} calculated from the models presented by Delzell et al.

Model	EC_{01} (ppm)	Potency estimate (ppm^{-1}) (i.e., $0.01/EC_{01}$)	LEC_{01} (ppm)	Potency estimate (ppm^{-1}) (i.e., $0.01/LEC_{01}$)
Multiplicative	1.12	8.9×10^{-3}	0.64	0.016
Power	0.57	0.018	0.066	0.15
Linear	1.16	8.7×10^{-3}	0.525	0.019
Initial square root	0.77	0.013	0.145	0.069
Final square root	0.45	0.022	0.12	0.083

As the estimates of choice, the MLEs of both the potency and EC_{01} are chosen. The main reason for this choice is that these estimates are based on human data from a large, well-conducted study. Although EPA has historically used upper-limit potency estimates for animal-to-human extrapolations, these upper limits derive their use more from computational instabilities of the MLEs in the quantitative risk models used. Human-to-human extrapolations typically use a simpler linear model form that does not have these instabilities. Furthermore, the human data inherently engender far less uncertainty in the risk estimates, so one may have more confidence in the use of MLEs from human data than from animal data.

9.2. CANCER RISK ESTIMATES BASED ON RODENT BIOASSAYS

9.2.1. Rat-Based Estimates

Cancer risk estimates based on the 1981 Hazelton rat inhalation study of 1,3-butadiene were presented in EPA's 1985 1,3-butadiene risk assessment (U.S. EPA, 1985). 95% upper-limit incremental lifetime unit cancer risk estimates for humans were calculated using the linearized multistage (LMS) model, after estimating the equivalent human dose assuming 1,3-butadiene retention based on results of a 1985 NTP absorption study (NTP, 1985; see EPA's 1985 report for further details). The upper limit based on the male rat tumor incidence data for Leydig cell tumors, pancreatic exocrine tumors, and/or Zymbal gland carcinomas was 4.2×10^{-3} per ppm 1,3-butadiene exposure. The upper limit based on the female rat tumor incidence data for mammary gland carcinomas, thyroid follicular tumors, and/or Zymbal gland carcinomas was 5.6×10^{-2} per ppm 1,3-butadiene exposure.

These rat-based estimates are not considered the most appropriate estimates of human risk; they are merely presented for comparison purposes. EPA believes that the mouse is likely to represent a better rodent model for human cancer risk from 1,3-butadiene (see below) and that the cancer risk estimates derived from the epidemiologic data are the best available estimates for human risk.

9.2.2. Mouse-Based Estimates

Cancer risk estimates based on the 1984 NTP mouse inhalation study were presented in EPA's 1985 1,3-butadiene risk assessment; however, revisions to these estimates are warranted because of the new data provided by the 1993 NTP mouse inhalation bioassay, which examined cancer response from exposure to lower 1,3-butadiene concentrations than those used in the 1984 study (NTP 1984, 1993; see Chapter 6). Groups of male and female $B6C3F_1$ mice were exposed to 1,3-butadiene concentrations of 0, 6.25, 20, 62.5, 200, or 625 ppm 1,3-butadiene for 6 hours/day, 5 days/week, for up to 104 weeks. Significant increases in tumor incidence were observed at multiple sites: the hematopoietic system (lymphomas; histiocytic sarcomas [males]), heart (hemangiosarcomas), lung, forestomach, Harderian gland, liver, preputial gland (males), ovary (females), and mammary gland (females), when adjusted for intercurrent mortality (Melnick and Huff, 1993). Significant increases in lung cancer incidence were observed in female mice at 1,3-butadiene exposure levels down to 6.25 ppm, the lowest level tested.

9.2.2.1. Quantal

When EPA estimates cancer risks for humans from rodent bioassay data, the risk estimates are generally calculated from the incidence of rodents of the most sensitive species, strain, and sex bearing tumors at any of the sites displaying treatment-attributable increases. In the case of 1,3-butadiene, so many sites demonstrated significant tumor increases attributable to 1,3-butadiene that background levels of tumor-bearing animals obfuscate the effects of 1,3-butadiene when all these tumor sites are combined. Therefore, risk estimates were derived from the incidence of female (most sensitive sex) mice with malignant lymphomas, heart hemangiosarcomas, lung tumors (alveolar/bronchiolar adenomas or carcinomas), mammary gland tumors (carcinomas, adenocanthomas, or malignant mixed tumors), or benign or malignant ovary granulosa cell tumors (Table 9-7). These sites were considered to be the most relevant sites with low background tumor incidence. Most of the impact on the low-dose linear extrapolation is from the lung tumor response, because the lung tumor incidences show the

Table 9-7. Dose-response data for linearized multistage model

Administered exposure (ppm)	Control	6.25	20	62.5	200
Human equivalent exposure (ppm)	0	1.1	3.6	11	36
Number of mice with tumors[a] / Number of mice at risk[b]	6/50	19/49	26/50	31/50	46/49

[a]Lymphocytic lymphomas, heart hemangiosarcomas, alveolar/bronchiolar adenomas or carcinomas, mammary gland tumors (carcinomas, adenocanthonomas, malignant mixed tumors), or benign or malignant ovary granulosa cell tumors.

[b]Female mice surviving to the time of the first significant tumor, which was a lymphocytic lymphoma at day 203.

largest increases at the lowest exposures. The 625 ppm exposure group was not included in the dose-response analysis because all of the mice were dead by week 65, and the tumor response was already virtually saturated in the 200 ppm exposure group. Note also that mice that died before the time of observation of the first tumor were considered to be not at risk and were excluded from the incidence denominators.

Human equivalent exposures were based on ppm 1,3-butadiene exposure, adjusted for continuous daily exposure (e.g., 6.25 ppm × 6/24 × 5/7 = 1.12 ppm). No attempt was made to adjust for internal doses of reactive 1,3-butadiene metabolites because the PBPK data were inadequate to develop reliable PBPK models (Chapter 8). No adjustments were made for 1,3-butadiene absorption because there are no adequate human data. Furthermore, there is no reason to expect nonlinearities in absorption at the lowest exposures (at least < 625 ppm).

A 95% upper-limit incremental lifetime unit cancer risk (extra risk) for humans was calculated from the incidence data in Table 9-7 using the LMS model. The multistage model has the form:

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where P(d) represents the lifetime risk (probability) of cancer at dose d, and parameters $q_i \geq 0$, for I=0, 1, ..., k. Extra risk over the background tumor rate is defined as

$$[P(d) - P(0)] / [1 - P(0)].$$

Point estimates of the dose coefficients (q_is), and consequently the extra risk function, at any dose d, are calculated by maximizing the likelihood function with respect to the tumor incidence data. The incremental lifetime unit cancer risk for humans (q_1^*) is defined as the 95% UCL on the parameter q_1, which is the linear dose coefficient, for extra risk. This 95% UCL represents a plausible upper bound for the true risk. The 95% UCL was calculated using the computer program GLOBAL86 (Howe and Van Landingham, 1986). Both the model and the curve-fitting methodology used are described in detail by Anderson et al. (1983).

The tumor incidence data in Table 9-7 generated the following results using the LMS model (GLOBAL86):

MLEs of dose coefficients:

$q_0 = 0.2629$

$q_1 = 0.07643$

$q_2 = 0.0$

$q_3 = 0.0$

$q_4 = 0.0$

p-value for chi-square goodness of fit > 0.01

$q_1^* = 0.10$

Thus, the incremental unit cancer risk estimate (95% UCL) for humans calculated from the mouse 1993 NTP inhalation bioassay results is 0.10 per ppm for continuous lifetime inhalation exposure to 1,3-butadiene. The MLE of risk appears to be nearly linear between 1 ppm and 1 ppb and is about 0.075 per ppm 1,3-butadiene exposure.

Under EPA's proposed new cancer risk assessment guidelines (U.S. EPA, 1996), unit cancer risk estimates for genotoxic chemicals, such as 1,3-butadiene, would be derived by straight linear extrapolation to 0 from the LED_{10} (estimated 95% UCL on the dose corresponding to a 10% cancer risk). Using the LEC_{10} generated for the LMS model by GLOBAL86 yields a unit cancer risk of 0.10/1.0 ppm = 0.10 per ppm, the same as the q_1^*. Using the EC_{10} yields $0.10/1.4 = 7.1 \times 10^{-2}$ per ppm.

MLE of risk for a dose of 1 ppm = 7.4×10^{-2}

MLE of risk for a dose of 1 ppb = 7.6×10^{-5}

MLE of dose for a risk of 0.10 (EC_{10}) = 1.4 ppm

95% UCL on dose for a risk of 0.10 (LEC_{10}) = 1.0 ppm

The unit cancer risk estimate (95% UCL) derived above is intended to depict a plausible upper limit on the risk of developing any 1,3-butadiene-attributable tumor over a full (70-year) lifetime. However, using the quantal incidence data for total tumor-bearing mice in each exposure group does not fully characterize the cancer potency reflected by the mouse bioassay

results. First, the methodology does not take into account the fact that many of the mice in the higher exposure groups had tumors at multiple significant sites. Second, the methodology ignores the fact that survival was significantly decreased in female mice exposed to 20 ppm or more 1,3-butadiene as a result of fatal 1,3-butadiene-attributable tumors. Time-to-tumor analyses conducted for specific tumor sites are presented below and can be used to evaluate the time component of the cancer risk.

9.2.2.2. Time-to-Tumor

The mouse inhalation bioassay results demonstrate different dose-response relationships for different tumor sites. To assess the characteristics of the dose-response relationships for different tumor sites, time-to-tumor analyses were performed to adjust for competing mortality from cancer at other sites.

Time-to-tumor analyses were conducted from the individual mice data, including the 9-month and 15-month interim sacrifice data, for sites demonstrating an increased cancer incidence. Benign and malignant tumors were combined for sites where appropriate. Thus time-to-tumor analyses were performed for lung alveolar/bronchiolar adenomas or carcinomas; lymphocytic lymphomas; heart hemangiosarcomas; hepatocellular adenomas or carcinomas; Harderian gland adenomas or carcinomas; forestomach squamous cell papillomas or carcinomas; malignant or benign ovary granulosa cell tumors (female); and mammary gland adenocanthomas, carcinomas, or malignant mixed tumors (female). Preputial gland carcinomas in male mice were not analyzed because not all the tissues were examined microscopically.

Data from the 625 ppm exposure groups were excluded from analysis because of excessive early mortality, as in the quantal analysis discussed above. In addition, data from interim sacrifices for specific sites were excluded for dose groups for which it appeared that complete histopathological examination for that site was not performed on the entire interim sacrifice group.

Human equivalent exposures were based on ppm 1,3-butadiene exposure, adjusted for continuous daily exposure, as described above.

The general model used for the time-to-tumor (or time-to-response) analyses was the multistage Weibull model, which has the form

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$$

where P(d,t) represents the probability of a tumor (or other response) by age t (in bioassay weeks) for dose d (human equivalent exposure), and parameters $z \geq 1$, $t_0 \geq 0$, and $q_i \geq 0$ for i=0, 1, ..., k, where k = the number of dose groups - 1. The parameter t_0 represents the time between when

a potentially fatal tumor becomes observable and when it causes death (see below). The analyses were conducted using the computer software TOX_RISK version 3.5 (Crump et al., ICF Kaiser International, Ruston, LA), which is based on Weibull models taken from Krewski et al. (1983). Parameters are estimated using the method of maximum likelihood.

Specific n-stage Weibull models were selected for the individual tumor types for each sex based on the values of the log likelihoods according to the strategy used by NIOSH (1991a). If twice the difference in log likelihoods was less than a chi-square with degrees of freedom equal to the difference in the number of stages included in the models being compared, then the models were considered comparable and the most parsimonious model (i.e., the lowest-stage model) was selected.

Tumor types were categorized by tumor context as either fatal or incidental tumors. Incidental tumors are those tumors thought not to have caused the death of an animal, while fatal tumors are thought to have resulted in animal death. Lymphocytic lymphomas, histiocytic sarcomas, and heart hemangiosarcomas were treated as fatal tumors, unless observed at an interim or terminal sacrifice, in which case they were considered incidental. Furthermore, these fatal tumors were deemed rapidly fatal, and t_0 was set equal to 0 (it was felt that there were insufficient data to reliably estimate t_0 in any event). Tumors at all other sites were treated as incidental. This is basically the same determination as that made by NIOSH (1991a), except the NIOSH report dealt with preliminary data that did not distinguish histiocytic sarcomas from lymphomas. NIOSH further cited the work of Portier et al. (1986) analyzing tumor types in NTP historical controls to lend support to these tumor context assumptions.

Parameter estimates for the time-to-tumor analyses for each tumor type are presented in Tables 9-8 (based on female mouse data) and 9-9 (male mice). For all tumor types except the heart hemangiosarcomas (both sexes) and the forestomach (male mice), the one-stage Weibull was the preferred model. For male mice, the heart hemangiosarcomas and forestomach tumors were best described by the two-stage model, while for female mouse heart hemangiosarcomas, a three-stage model was preferred.

Human unit cancer risk (or potency) estimate results (extra risk) are presented in Tables 9-10 (based on female mouse data) and 9-11 (male mice). Mouse lung tumors convey the greatest amount of extrapolated risk to humans from both the female mouse data (q_1^* = 0.14/ppm 1,3-butadiene exposure) and the male mouse data (q_1^* = 0.10/ppm). Note that the unit risk estimate of 0.14/ppm generated from the female mouse lung tumor data using a time-to-tumor

Table 9-8. Parameter estimates for multistage Weibull time-to-tumor model based on female mouse tumor incidence, w/o 625 ppm group

Tissue	Q0	Q1	Q2	Q3	Z
Lymphocytic lymphoma	6.23×10^{-10}	1.67×10^{-10}	-	-	3.92
Heart hemangiosarcoma	0	0	0	2.88×10^{-17}	6.10
Lung	5.83×10^{-9}	3.40×10^{-9}	-	-	3.69
Mammary	2.47×10^{-6}	5.42×10^{-5}	-	-	1.27
Liver	2.12×10^{-8}	2.11×10^{-9}	-	-	3.58
Forestomach	0	1.29×10^{-9}	-	-	3.43
Harderian gland	1.50×10^{-5}	2.06×10^{-6}	-	-	2.03
Ovary	7.83×10^{-9}	1.48×10^{-8}	-	-	3.05
Histiocytic sarcoma	3.68×10^{-14}	1.23×10^{-14}	-	-	6.03

Table 9-9. Parameter estimates for multistage Weibull time-to-tumor model based on male mouse tumor incidence, w/o 625 ppm group

Tissue	Q0	Q1	Q2	Z
Lymphocytic lymphoma	1.84×10^{-8}	1.28×10^{-9}	-	3.08
Heart hemangiosarcoma	0.0	0.0	1.14×10^{-23}	10.0
Lung	1.38×10^{-7}	9.53×10^{-8}	-	3.27
Liver	1.40×10^{-4}	5.57×10^{-6}	-	1.83
Forestomach	9.68×10^{-10}	0.0	3.83×10^{-11}	3.39
Harderian gland	1.65×10^{-7}	7.45×10^{-8}	-	2.90
Histiocytic sarcoma	0.0	1.04×10^{-13}	-	5.50

Table 9-10. Human unit cancer risk estimates (extra risk, computed for risks of 10^{-6}) based on female mouse tumor incidences, w/o 625 ppm group using multistage Weibull time-to-tumor model

Tissue	Q1* (ppm^{-1})	MLE (ppm^{-1})	EC_{10} (ppm)	LEC_{10} (ppm)	$0.1/LEC_{10}$ (ppm^{-1})
Lymphocytic lymphoma	0.0239	0.0128	8.08	4.33	0.0231
Heart hemangiosarcoma	4.27×10^{-3}	3.99×10^{-6}	11.6	9.24	0.0108
Lung	0.1404	0.0980	1.06	0.737	0.1357
Mammary	0.0321	0.0203	5.09	3.23	0.0310
Liver	0.0631	0.0366	2.82	1.64	0.0610
Forestomach	0.0215	0.0112	9.22	4.80	0.0208
Harderian gland	0.0443	0.0258	4.00	2.33	0.0429
Ovary	0.0358	0.0218	4.74	2.89	0.0346
Histiocytic sarcoma	0.1283	3.36×10^{-3}	30.8	0.806	0.1241

Table 9-11. Human unit cancer risk estimates (extra risk, computed for risks of 10^{-6}) based on male mouse tumor incidences, w/o 625 ppm group using multistage Weibull time-to-tumor model

Tissue	Q1* (ppm^{-1})	MLE (ppm^{-1})	EC_{10} (ppm)	LEC_{10} (ppm)	$0.1/LEC_{10}$ (ppm^{-1})
Lymphocytic lymphoma	6.437×10^{-3}	2.220×10^{-3}	46.6	16.1	6.224×10^{-3}
Heart hemangiosarcoma	0.01266	4.040×10^{-3}	12.0	7.59	0.01318
Lung	0.1023	0.06998	1.48	1.01	0.09890
Liver	0.04447	0.02720	3.80	2.33	0.04300
Forestomach	4.258×10^{-3}	1.660×10^{-5}	19.2	13.3	7.517×10^{-3}
Harderian gland	0.07402	0.05398	1.92	1.40	0.07157
Histiocytic sarcoma	0.02162	0.01394	7.42	4.78	0.02090

model is greater than the unit risk estimate of 0.10/ppm generated above from multiple female mouse tumor sites when only the quantal data were used and decreased survival time was not taken into account.

Although the time-to-tumor modeling does help account for decreased survival times in the mice, considering the tumor sites individually does not convey the total amount of risk potentially arising from the sensitivity of multiple sites. To get some indication of the total unit risk from multiple tumor sites, assuming the multiple sites are mechanistically independent, the MLEs of the unit potency from the Weibull time-to-tumor models were summed across tumor sites and estimates of the 95% upper bound on the summed unit potency were calculated. The TOX_RISK software provides MLEs and 95% UCL's for human risk at various exposure levels, allowing for the calculation of unit potency estimates at those exposure levels.

When the MLEs of unit potency calculated at 1 ppb from the female mouse data were summed across the female mouse tumor sites, the MLE of the total unit risk was 0.23/ppm continuous lifetime 1,3-butadiene exposure. A 95% upper bound for the total potency was calculated by assuming a normal distribution for the risk estimates, deriving the variance of the risk estimate for each tumor site from its 95% UCL according to the formula

$$95\%\ UCL = MLE + 1.645\sigma,$$

where the standard deviation σ is the square root of the variance, summing the variances across tumor sites to obtain the variance of the sum of the MLEs, and calculating the 95% UCL on the sum from the variance of the sum using the same formula. The resulting 95% UCL on the unit potency for the total unit risk was 0.38/ppm. In comparison, summing the q_1*s across the female mouse tumor sites yielded 0.50/ppm.

The unit potencies were also summed using a Monte Carlo analysis and the software Crystal Ball version 4.0 (Decisioneering, Denver, CO). Normal distributions were assumed for the unit potency for each tumor site, with the mean equal to the MLE and σ as calculated from the above formula. A distribution around the sum of the MLEs was then generated by simulating the sum of unit potencies picked from the distributions for each tumor site (according to probabilities determined by those distributions) 10,000 times. The mean for the sum and the 95th percentile on the distribution were the same as the sum of MLEs and 95% UCL calculated above, as they should be. However, a sensitivity analysis based on the contribution to variance revealed that variability associated with the unit potency estimate for the histiocytic sarcomas was contributing more than 83% of the variance on the sum, and some of the simulated sums were negative (the distributions for the unit potency estimates were not constrained for the summation analyses). Excluding the histiocytic sarcomas yielded the same MLE of total risk of

0.23/ppm; however, the 95% UCL decreased to 0.29/ppm. The lung, which then contributes the most to the sum, contributed about 55% of the variance, followed by the liver with 20%, and no simulated sums were negative.

The same analyses were performed summing the estimates of unit potency derived from the male mouse data for the different tumor sites. The resulting MLE for the total unit risk was 0.18/ppm lifetime 1,3-butadiene exposure with a 95% UCL of 0.22/ppm. The lung contributed about 56% to the variance, followed by the Harderian gland with about 20%. Histiocytic sarcomas contributed only 3% in this case, and all simulated sums were positive.

Finally, the summation analyses were repeated for unit potency estimates calculated at 1 ppm exposure for comparison with the estimates calculated at 1 ppb. For the female mouse-based risks (excluding histiocytic sarcomas), the sum of the MLEs was 0.22/ppm (2% lower than at 1 ppb) and the 95% UCL on the sum was 0.28/ppm (4% lower than at 1 ppb). Thus, the total unit potency estimates are reasonably linear up to 1 ppm continuous lifetime exposure. Recall from Table 9-8 that the selected model for the heart hemangiosarcomas in the female mouse was nonlinear; however, the unit risk estimates based on the heart hemangiosarcomas at these extrapolated doses are lower than for the other sites and do not affect the total risk summed across tumor sites. Similarly, the male mouse based- results (both the sum of the MLEs and the 95% UCL on the sum) calculated at 1 ppm were 2% lower than those calculated at 1 ppb. For the male mice, the selected models for both the heart hemangiosarcomas and the forestomach tumors were nonlinear (Table 9-9); however, as with the female heart hemangiosarcomas, the risks from these sites have little impact on the total risk.

The results of these summation analyses are summarized in Table 9-12.

9.2.3. Discussion

Based on the analyses discussed above, the best estimate for an upper bound on human extra cancer risk from continuous lifetime exposure to 1,3-butadiene derived from animal data is about 0.3/ppm. This estimate reflects the time-to-tumor response as well as the exposure-response relationships for the multiple tumor sites (excluding histiocytic sarcomas) in the most sensitive species and sex (the female mouse). Histiocytic sarcomas were excluded because they introduced excessive variance into the upper bound while contributing only negligibly to the MLE of total unit risk.

The greatest source of uncertainty in this estimate is from the interspecies extrapolation of risk from the mouse to humans. The two rodent species for which bioassay data were

Table 9-12. Unit potency estimates (extra risk) summed across tumor sites

	Sum of MLEs (ppm^{-1})	95% UCL on sum (ppm^{-1})	Sum of q_1*s (ppm^{-1})
Female mouse tumor sites (calculated at 1 ppb)	0.23	0.38	0.50
Female sites excluding histiocytic sarcomas (at 1 ppb)	0.23	0.29	0.37
Female sites excluding histiocytic sarcomas (at 1 ppm)	0.22	0.28	0.36
Male mouse tumor sites (at 1 ppb)	0.18	0.22	0.27
Male mouse tumor sites (at 1 ppm)	0.17	0.21	0.26

available**C**the mouse and the rat**C**varied significantly in their carcinogenic responses to 1,3-butadiene, in terms of both site specificity and degree of response (Chapter 6). The mouse and rat also exhibit substantial quantitative differences in their metabolism of 1,3-butadiene to potentially reactive metabolites (Chapter 3). Unfortunately, existing pharmacokinetic models have been unable to explain the species differences in carcinogenic response (Chapter 8), and it is likely that there are pharmacodynamic as well as pharmacokinetic differences between the mouse and rat with respect to their sensitivities to 1,3-butadiene.

The mouse was the more sensitive species to the carcinogenic effects of 1,3-butadiene exposure and, hence, the more conservative (public health protective) for the extrapolation of risk to humans. In addition, the mouse appears to be the more relevant species for extrapolation to humans in terms of site specificity, as 1,3-butadiene induces tumors of the lymphohematopoietic system in both mice and humans. Melnick and Kohn (1995) further suggest that the genetic mutations observed in 1,3-butadiene-induced mouse tumors are analogous to genetic alterations frequently observed in human tumors.

In addition to uncertainties pertaining to the relevance of the rodent models to human risk, there is uncertainty in quantitatively scaling the animal risks to humans. Ideally, a PBPK model for the internal dose of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation; however, current PBPK models are inadequate for this purpose (Chapter 8). In vitro metabolism data for humans suggest that interhuman variability in the capacity to metabolically activate 1,3-butadiene nearly spans the range between rats and mice (Chapter 3).

Another major source of uncertainty in the unit potency estimate of 0.3/ppm is the extrapolation of high-dose risks observed in the mouse bioassay to lower doses that would be of concern from human environmental exposures. A multistage Weibull time-to-tumor model was the preferred model because it can take into account the differences in mortality between the exposure groups in the mouse bioassay; however, it is unknown how well this model is predicting the low-dose extrapolated risks for 1,3-butadiene.

There are also uncertainties pertaining to the specific assumptions used in conducting these multistage Weibull time-to-tumor analyses. Some alternative analyses were performed to consider the sensitivity of the results to some of these assumptions. For example, for each of the tumor types assumed to be fatal, alternative analyses were conducted in which the modeling software estimated t_0. In each case, the resulting q_1*s, EC_{10}s, and LEC_{10}s were identical to those generated when t_0 was set equal to 0 a priori.

In addition, analyses were performed on the lymphocytic lymphoma data including the 625 ppm group, as this was the exposure group most affected by lymphocytic lymphomas and relatively few animals in this group survived to develop tumors at other sites. From the female mouse data, the resulting q_1* was 0.515/ppm, or roughly twice that calculated when the 625 ppm group was excluded. From male mice, the q_1* was 0.0215/ppm, or roughly 3 times higher than that obtained when the 625 ppm group was excluded.

NIOSH (1991a) examined the sensitivity of its results for each tumor type to (1) model selection (i.e., stage of Weibull model) from among models deemed to be comparable, (2) tumor context assumptions, and (3) exclusion/inclusion of the 625 ppm exposure group, and generally found only small discrepancies in the results. Moreover, uncertainties in some of the model assumptions are trivial compared with the major uncertainties introduced by the interspecies and high-to-low dose extrapolations.

In conclusion, because of the high uncertainty in extrapolating 1,3-butadiene cancer risks from rodents to humans and the existence of good-quality occupational epidemiology data with exposure measures, the epidemiology-based risk estimates presented at the beginning of this chapter are the preferred human risk estimates. The rodent-based estimates are presented primarily for comparison purposes. Realizing that different quantitative methodologies and assumptions were used to calculate the various risk estimates, recall that the estimated upper bound (95% UCL) on human incremental lifetime unit cancer risk from continuous 1,3-butadiene exposure was 6×10^{-2}/ppm based on the female rat tumors, 3×10^{-1}/ppm based on the female mouse tumors, and 2×10^{-2}/ppm and 6×10^{-3}/ppm based on lymphocytic lymphomas in female and male mice, respectively (lymphocytic lymphomas being the tumor site that most closely resembles the lymphohematopoietic cancers observed in male workers exposed to 1,3-butadiene). The best estimate (MLE) of human incremental lifetime unit cancer risk

extrapolated from the leukemias observed in occupational epidemiology studies was 9×10^{-3}/ppm.

9.3. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

9.3.1. Introduction

The reproductive and developmental effects of 1,3-butadiene are among the effects (both cancer and noncancer) observed at the lowest exposure levels following short-term or chronic inhalation exposure. Data on reproductive and developmental effects were available from three types of studies for modeling and calculation of a benchmark concentration (BMC). In the first type of study, developmental toxicity of 1,3-butadiene was evaluated in studies in mice and rats that included 10-day exposures via inhalation at 0, 40, 200, and 1,000 ppm on gestation days (gd) 6-15 for 6 h/day (Hackett et al., 1987a, b). In rats, no effects were detected at any exposure level for developmental toxicity (200 ppm was the NOAEL for maternal toxicity), while reduced fetal weights were seen in mice at all exposure levels (Table 9-13). Thus, 40 ppm was considered a LOAEL for mice.

In the second type of study, male-mediated effects of 1,3-butadiene were evaluated in a dominant lethal study in which CD-1 mice were exposed to 0, 12.5, or 1,250 ppm for 6 h/day, 5 days/week, 10 weeks (Anderson et al., 1993, 1995). One group of females at each exposure level was killed on gd 17, while another was allowed to litter. At 12.5 ppm, the frequency of late deaths and congenital abnormalities on gd 17 were increased, while in litters allowed to deliver their pups, changes in implantation numbers, postimplantation loss, litter size, and weight at birth and at weaning were significantly different only at 1,250 ppm. In addition, body weights of F_1 males at all time points and of F_1 females at several time points between 8 and 71 weeks of age were significantly increased above controls at both 12.5 ppm and 1,250 ppm. Based on the data from animals killed on gd 17, there was no NOAEL for dominant lethal effects in the study (Table 9-14).

In the third type of study, reproductive effects of 1,3-butadiene were seen in lifetime studies in mice after chronic inhalation exposure to 6.25, 20, 62.5, 200, and 625 ppm for 6 h/day, 5 days/week (NTP, 1993). The lowest exposure level studied in mice (6.25 ppm) showed increased ovarian atrophy and was considered a LOAEL (Table 9-15). Minimal data from studies on rats suggested their lesser sensitivity to chronic exposure than for mice in that effects on fertility were noted only at high exposure levels (600 ppm and above).

Table 9-13. Prenatal (developmental) toxicity study (Hackett et al., 1987b)

Species/strain: Pregnant CD-1 mice
Exposure time: Gestational day (GD) 6-15
Exposure regimen: 6 h/day
Exposure levels: 0, 40, 200, or 1,000 ppm

Fetal Weight Data

Exposure level	No. litters	Mean fetal weight/litter
0	18	1.341
40 ppm	19	1.282
200 ppm	21	1.126
1000 ppm	20	1.038

Table 9-14. Male-mediated developmental toxicity (Anderson et al., 1993, 1995)

Species/strain: CD-1 mice, adult males
Exposure time: 10 weeks
Exposure regimen: 6 h/day, 5 days/week
Exposure levels: 0, 12.5 ppm, 1250 ppm

Exposure level	Number exposed	No. implants (no. preg. females)	% Early and late deaths	% Live implants
0	25	12.09 (23)	4.68	94.6
12.5 ppm	25	12.75 (24)	7.52	92.2
1250 ppm	50	10.68 (38)	22.91	76.8
Exposure level	Mean litter size at birth (no. litters)	Mean no. implants (no. litters)	% Post-implantation loss	Mean litter size at weaning (no. litters)
0	12.22 (18)	12.81 (16)	4.88	12.17 (18)
12.5 ppm	11.14 (21)	12.35 (17)	9.05	10.95 (20)
1250 ppm	9.06 (33)	10.47 (32)	23.88	9.03 (33)

Table 9-15. NTP chronic study (1993)

Species/strain: Male and female $B6C3F_1$ mice
Exposure regimen: 6 h/day, 5 days/week for 2 years
Exposure levels: 0, 6.25, 20, 62.5, 200, or 625 ppm

Incidence Data - Ovarian Atrophy

Exposure level	Ovarian atrophy-9 mo		Ovarian atrophy-15 mo		Ovarian atrophy-2 years	
	No. examined	% Affected	No. examined	% Affected	No. examined	% Affected
0	10	0	10	0	49	8.16
6.25 ppm	--	--	10	0	49	38.78
20.00 ppm	--	--	10	10	48	66.67
62.50 ppm	10	0	10	90	50	84.00
200.00 ppm	10	90	10	70	50	86.00
625.00 ppm	8	100	2	100	79	87.34

Ovarian Atrophy - Lesion Distribution
Number (%)

Exposure level	Ovarian atrophy-9 mo			Ovarian atrophy-15 mo			Ovarian atrophy-2 years			
	Minimal	Mild	Moderate	Minimal	Mild	Moderate	Minimal	Mild	Moderate	Marked
0.00	0	0	0	0	0	0	1 (2)	2 (4)	1 (2)	0
6.25 ppm	--	--	--	0	0	0	0	15 (31)	4 (8)	0
20.00 ppm	--	--	--	1 (10)	0	0	1 (2)	23 (48)	8 (17)	0
62.50 ppm	0	0	0	1 (10)	7 (70)	1 (10)	3 (6)	18 (36)	21 (42)	0
200.00 ppm	0	0	9 (90)	0	1 (10)	6 (60)	0	9 (18)	34 (18)	0
625.00 ppm	0	0	8 (100)	0	0	2 (100)	0	19 (24)	47 (59)	3 (4)

Table 9-15. NTP chronic study (1993) (continued)

Incidence Data - Uterine and Testicular Atrophy

Exposure level	Uterine atrophy-9 mo		Uterine atrophy-15 mo		Uterine atrophy-2 years	
	No. examined	No. (%) Affected	No. examined	No. (%) Affected	No. examined	No. (%) Affected
0	10	0	10	0	50	1 (2)
6.25 ppm	--	--	1	0	49	0
20 ppm	--	--	10	0	50	1 (2)
62.5 ppm	10	0	10	0	49	1 (2)
200 ppm	10	3 (30)	10	0	50	8 (16)
625 ppm	8	6 (75)	2	2 (100)	78	41 (53)

Exposure level	Testicular atrophy-9 mo		Testicular atrophy-15 mo		Testicular atrophy-2 years	
	No. examined	No. (%) Affected	No. examined	No. (%) Affected	No. examined	No. (%) Affected
0	10	0	10	0	50	1 (2)
6.25 ppm	--	--	--	--	50	3 (6)
20 ppm	--	--	1	0	50	4(8)
62.5 ppm	--	--	--	--	48	2 (4)
200 ppm	10	0	10	0	49	6 (12)
625 ppm	10	6 (60)	7	4 (57)	72	53 (74)

In conclusion, each of these three types of studies indicated the potential for 1,3-butadiene to affect reproduction and development in mice at low levels of exposure.

9.3.2. Fetal Weight Modeling

Fetal weight data (Table 9-13) were fit using a log-logistic model for developmental toxicity, as described by Allen et al. (1994a). The TERALOG model software (ICF Kaiser International, KS Crump Group) was used for this purpose. This model allows for nesting of fetal data within litters and takes into account intralitter correlations and litter size. To apply this model, the individual fetal weights were converted to dichotomous data using two different values as the cutoff for defining an adverse level of response:

(1) a decrease below the 5th percentile of the control distribution, or

(2) a decrease below the 10th percentile.

The model was used to estimate: (a) the EC_{05}* and the LEC_{05}** associated with a 5% additional risk of obtaining a fetal weight below the 5th percentile of the controls, or (b) the EC_{10} and LEC_{10} associated with a 10% additional risk of obtaining a fetal weight below the 10th percentile of controls, based on Kavlock et al. (1995). The model can be expressed as:

$$P(d, s) = \alpha + \theta_1 s + [1 - \alpha - \theta_1 s]/\{1 + \exp[\beta + \theta_2 s - \gamma \log (d-d_0)]\}$$

where P(d, s) is the probability of a low-weight fetus at dose d and litter size s, and the parameters α, β, γ, θ_1, and θ_2 are estimated by methods of maximum likelihood. In order to get an acceptable fit, an intercept parameter (d_0) was included in the model (sometimes referred to as a threshold parameter, i.e., the point at which the model can no longer distinguish from background). The parameter constraints were: $d_0 \geq 0$; $\gamma \geq 1$; $0 \leq \propto - \theta_1 s \leq 1$.

Fetal weight also was modeled as the average of mean fetal weights per litter using the continuous power model (Allen et al., 1994b). The THWC model software (ICF Kaiser International, KS Crump Group) was used for this purpose. Several cutoff values were used, based on Kavlock et al. (1995):

(1) a 5% reduction in mean fetus weight/litter from the control mean,

---

*The EC is the effective (exposure) concentration associated with a given level of risk, 5% in this case.

**The LEC is the lower confidence limit on the effective concentration associated with a given level of risk. The LEC is also known as the benchmark concentration.

(2) a reduction in mean fetus weight/litter to the 25th percentile of the control distribution, and

(3) a reduction in mean fetus weight/litter to 0.5 SD below the control mean.

The continuous power model can be expressed as:

$$m(d) = \alpha + \beta d^{\gamma},$$

where m(d) is the mean of the mean fetus weight/litter for dose d, and α, β, and γ are parameters estimated by maximum likelihood methods. The parameter constraints were: $\alpha \geq 0$; $\gamma \geq 1$.

Goodness of fit was determined by a χ^2 test for the log-logistic model, and by an F test for the continuous power model (U.S. EPA, 1995, Appendix A). The model was considered to provide an acceptable fit if the p value was greater than 0.05 and a graphical display of the data showed a good fit of the model.

A third approach used to model fetal weight data was the hybrid approach proposed by Gaylor and Slikker (1990) and further developed by Crump (1995). The BENCH_C model software (ICF Kaiser International, KS Crump Group) was used for this purpose. This approach uses all of the information contained in the original observations by modeling changes in mean response as a function of exposure concentration, but defines ECs and LECs in terms of probability of response. The continuous data are fit using a model that incorporates parameters from the quantal model. Several models are possible within the software for both continuous data and quantal risk estimates. For this study, the log-logistic model (not including litter size) was used for the quantal risk estimates and the following model for the continuous portion of the hybrid model:

$$m(d) = m(0) + \sigma[N^{-1}(1-P_0) - N^{-1}\{(1-P_0)[-1/[1+(\beta d^k)]]\}]$$

where N is the standard normal distribution function, m(d) is the mean response at dose d, σ is the standard deviation of the response fixed for all dose groups, and β and k are the log-logistic model parameters estimated by the maximum likelihood method. The parameter constraints were: $k \geq 1$; $\beta \geq 0$.

Crump (1995) indicated that a background rate (P_0) of 5% and an EC corresponding to 10% additional risk corresponds to a change from the control mean of 0.61 SD. Since a change in mean fetal weight/litter of 0.5 SD corresponded on average to a NOAEL in studies by Kavlock et al. (1995), a P_0 of 0.05 and an EC_{10} (10% additional risk) were used here.

Results of the modeling approaches for fetal weight are shown in Table 9-16 and Figures 9-6 to 9-8. The log-logistic model resulted in an adequate fit of the data. Since the log-logistic model requires converting continuous data to quantal responses, the continuous power model was also applied, but did not give an adequate fit with all four exposure levels. When fit to the first three exposure levels, an adequate fit was obtained. The continuous power model gave similar ECs and LECs but these were somewhat larger than those obtained with the log-logistic model except for the one based on a cutoff using the 25th percentile. The hybrid approach resulted in a quantal estimate of dose at the LEC_{10} that was lower than that for either the log-logistic or continuous power model.

All three models have strengths and limitations that must be considered. The log-logistic model accounts for intralitter correlation and litter size, but requires conversion of continuous data to quantal responses. Neither the continuous power nor the hybrid model are currently structured to account for intralitter correlation or litter size. The version of the hybrid model used here does not allow use of the standard deviation (σ) for individual dose groups, so the σ at dose d_0 was used for all dose groups. The continuous power and hybrid models take advantage of the power of modeling the continuous data, but the hybrid model expresses the EC and LEC as a quantal estimate of risk, allowing direct comparison with ECs and LECs for quantal endpoints. Given the various advantages and limitations of these models, the hybrid model is considered the preferred approach for modeling continuous data.

Table 9-16. Fetal weight modeling (LOAEL = 40 ppm)

Model	Response	Cutoff	EC	LEC	p-Value
Log-logistic (1-4)[a]	Individual fetal weight	5th percentile	EC_{05} = 46.85	LEC_{05} = 27.02	0.079
		10th percentile	EC_{10} = 49.69	LEC_{10} = 38.89	0.067
Continuous power (1-3)[a]	Mean fetal weight/litter	5% relative reduction	65.08	53.51	0.77
		25th percentile	45.10	36.66	
		0.5 SD absolute reduction	50.99	41.44	
Hybrid model[a] (1-4)	Mean fetal weight/litter	P_0 = 0.05	EC_{10} = 28.19	LEC_{10} = 13.67	0.08

[a]Exposure levels modeled in each case are shown in parentheses.

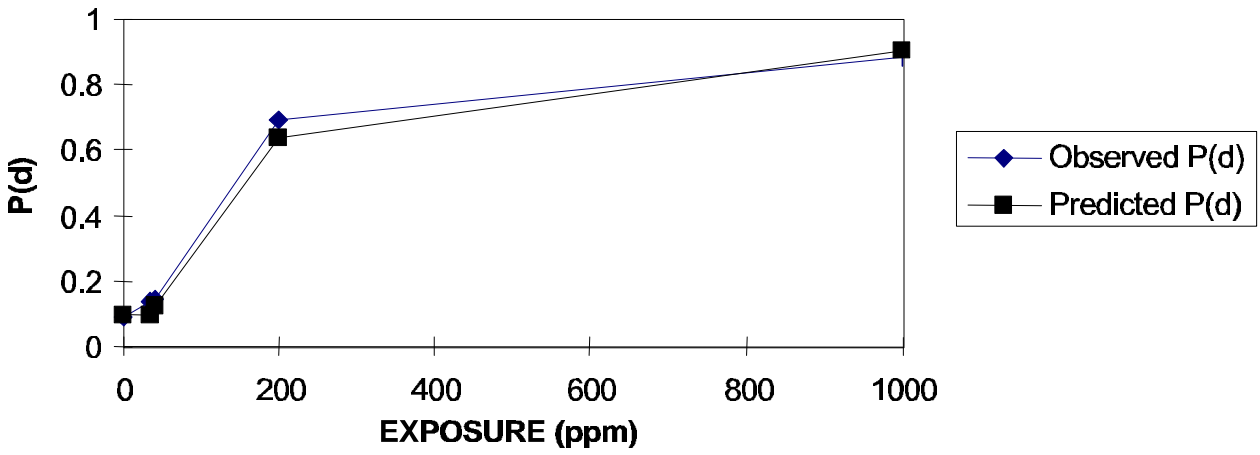
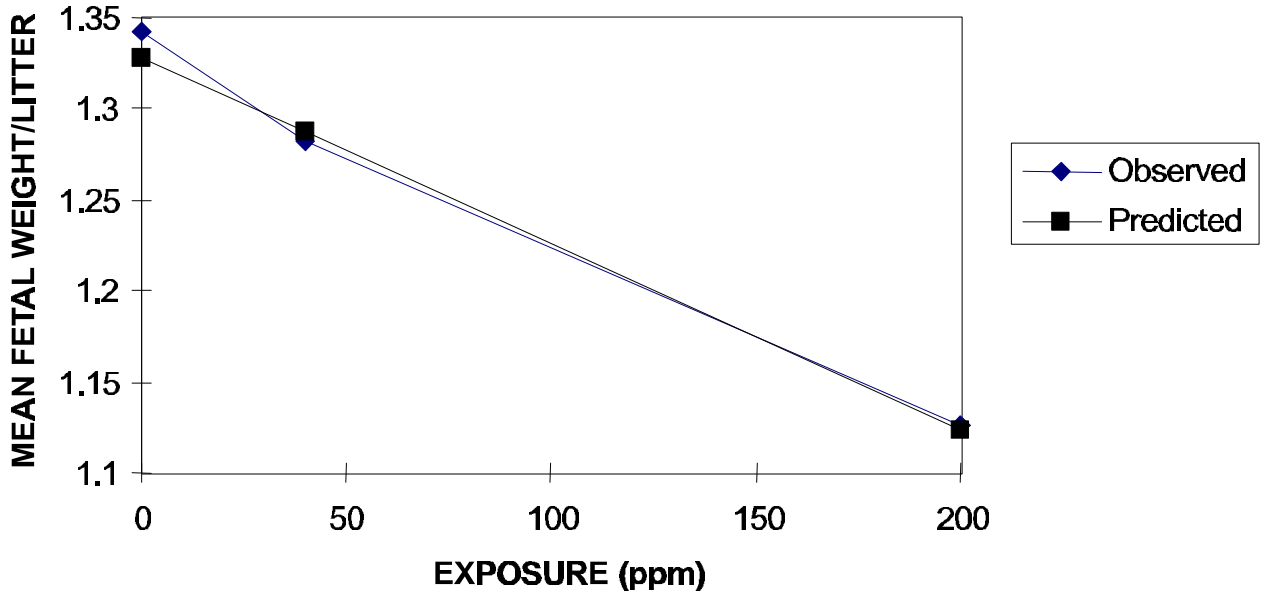


Figure 9-6. Observed versus predicted dose (exposure) probability P(d) of fetal weight reduction below the 10th percentile of controls using log-logistic model.

Figure 9-7. Observed versus predicted mean fetal weight per litter using continuous model.



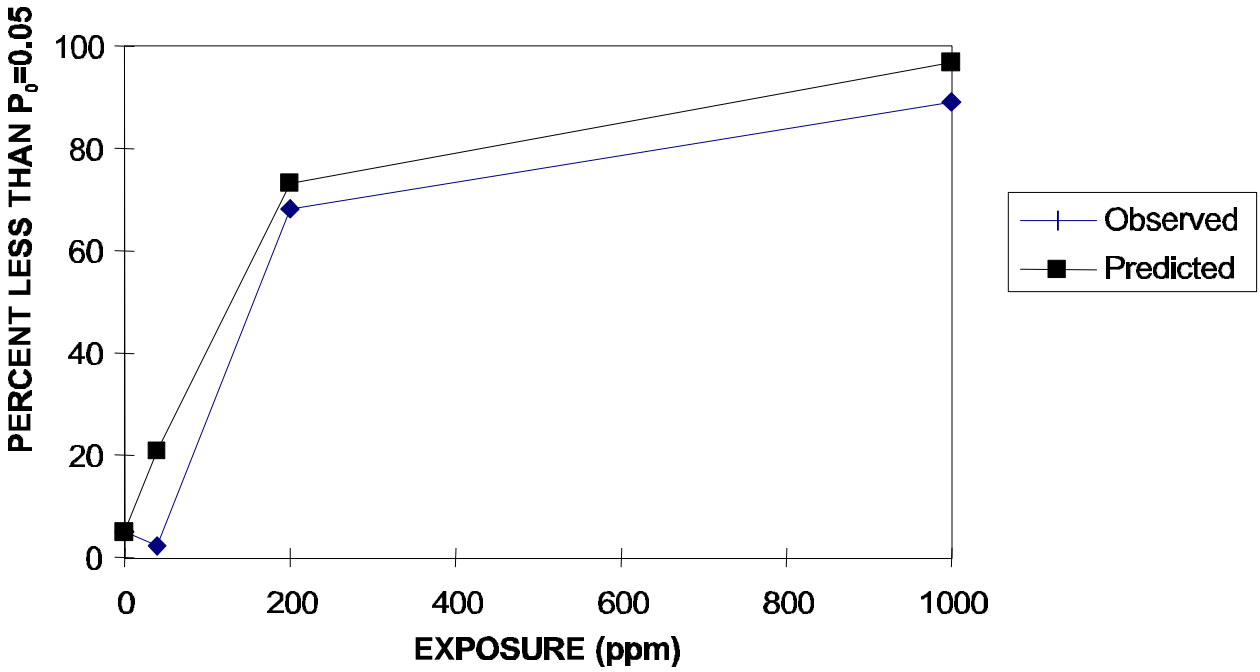


Figure 9-8. Observed versus predicted percent of mean fetal weights per litter less than the 5th percentile of controls ($P_0 = 0.05$) using hybrid model.

9.3.3. Male-Mediated Developmental Toxicity Modeling

Several endpoints from animals killed at gd 17 and after birth were modeled using a log-linear model:

$$y(d) = \alpha + \beta x [\ln(1 + d)]$$

This model was used because of the wide spacing of doses and the lack of linearity in the dose-response relationship. The data were limited in that only two exposure levels in addition to controls were used, and the exposure levels differed by two orders of magnitude.

Although a statistically significant effect was noted at 12.5 ppm and 1,250 ppm for the incidence of late deaths in the original paper (Anderson et al., 1993), the response in late deaths at the higher exposure level was lower than at 12.5 ppm, probably because there were so many early deaths at the higher level. For the same reason, the incidence of congenital abnormalities was higher at 12.5 ppm than at 1,250 ppm. When early and late deaths were combined, a consistently increasing response with increasing exposure level was seen. When combined, the incidence in the controls was increased from 0 to 13 (4.68% of total implants), while in the 12.5 ppm group the incidence increased from 7 (2.29%) to 23 (7.52%).

Unfortunately, fetal weights were not reported in the prenatal portion of the dominant lethal study, and only total litter weights (which are confounded by the number of live pups) were reported in the postnatal portion of the study. When mean pup weight per litter was calculated, there was no difference among F_1 controls and treated offspring, and in some cases, a slight increase was seen (data not shown). This is interesting in light of the fact that treated F_1 male and female weights were increased above controls at 8 through 71 weeks of age. No modeling of these data was conducted.

Table 9-17 shows the results of modeling the dominant lethal data. The ECs and LECs for both 5% and 10% responses are shown. The log-linear model gave a good fit for all the data except for the number of implants in the prenatal study (see Figures 9-9 to 9-15; note that "dose" refers to 24-h adjusted exposure). This apparently was due to the fact that the number of implants was somewhat higher in the 12.5 ppm group than in controls or the 1,250 ppm group. Given that these data are from fetuses or pups within litters, it is likely that an EC_{05} and LEC_{05} can be estimated from the data with some degree of reliability. Also, based on the studies of Allen et al. (1994a and b), the LEC_{05} (BMC_{05}) for such endpoints was similar to the NOAEL on average. Although certain endpoints not modeled here (late fetal deaths and congenital malformations) were statistically increased in both the 12.5 ppm and 1,250 ppm exposure

Table 9-17. ECs and LECs for male-mediated developmental toxicity [a]

	Prenatal data			Postnatal data			
Estimate	No. implants	Early and late deaths	Live implants	No. implants	Post-implantation loss	Litter size at birth	Litter size at weaning
EC_{05}	0.21	3.4	3.5	0.12	3.2	0.1	0.1
LEC_{05}	0.12	2.4	2.4	0.08	2.2	0.07	0.07
EC_{10}	0.47	18	19	0.26	16	0.20	0.20
LEC_{10}	0.26	10	11	0.17	9.0	0.15	0.15
p-Value	0.12	0.66	0.99	0.95	0.99	0.54	0.45
NOAEL	220 ppm	2.2 ppm	2.2 ppm	220 ppm	2.2 ppm	2.2 ppm	2.2 ppm

[a]Exposures were adjusted to 24-h daily exposures (e.g., $12.5\left(\frac{6}{24}\right)\left(\frac{5}{7}\right) = 2.2$ ppm).

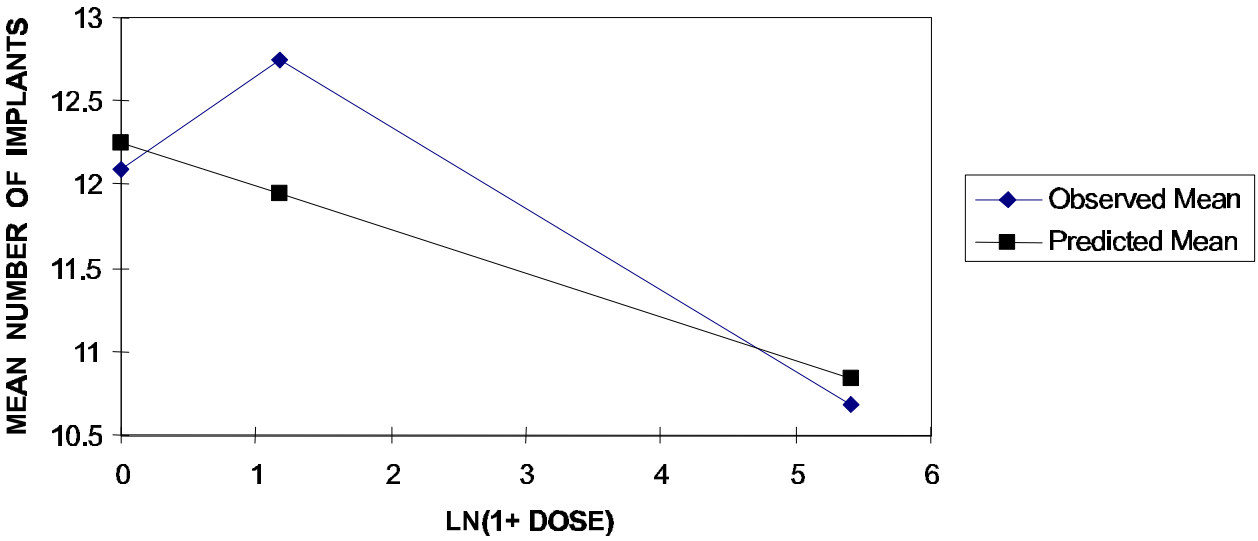
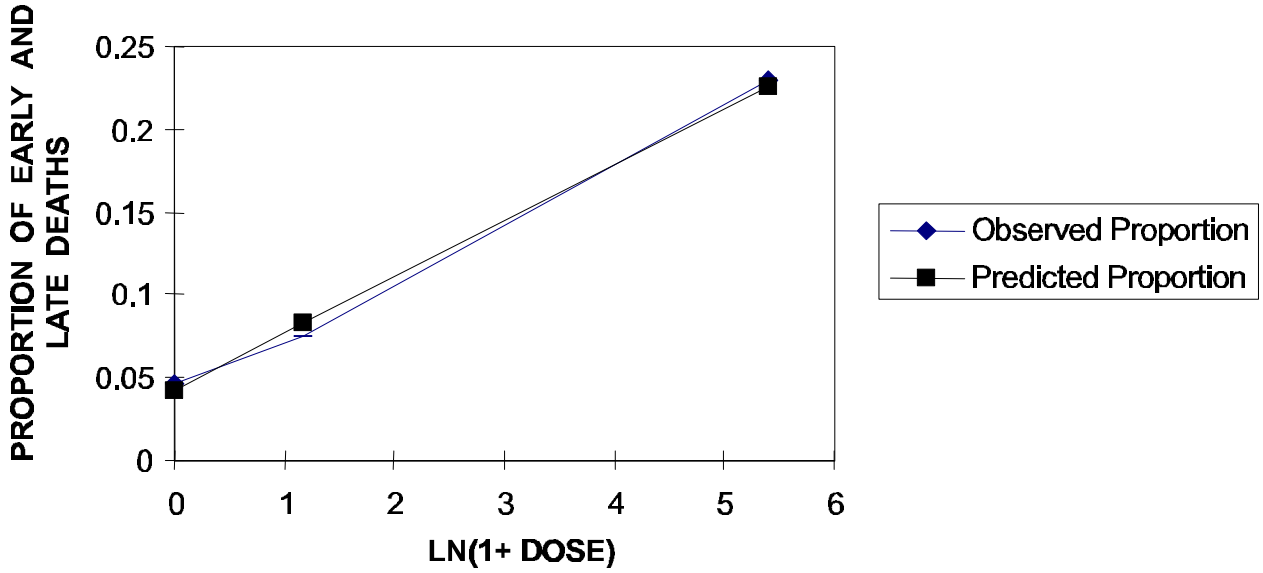


Figure 9-9. Observed versus predicted mean number of implants (prenatal) using log-linear model.

Figure 9-10. Observed versus predicted proportion of early and late deaths per implantation (prenatal) using log-linear model .



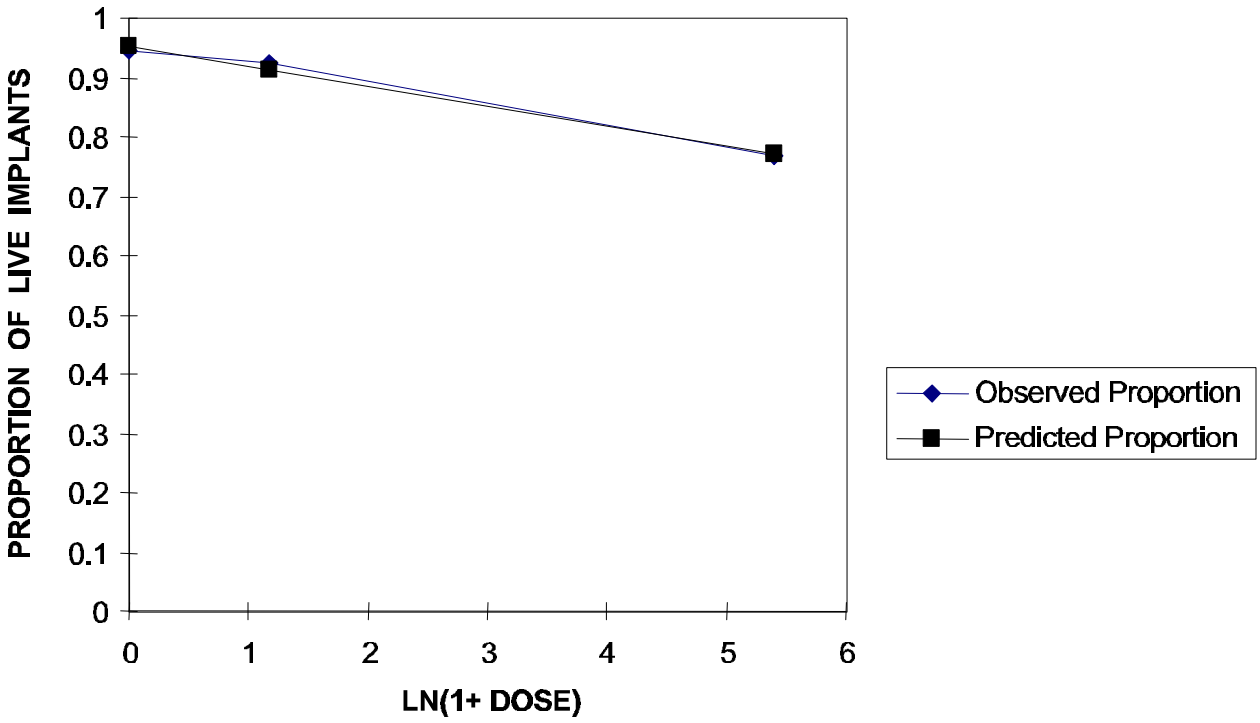
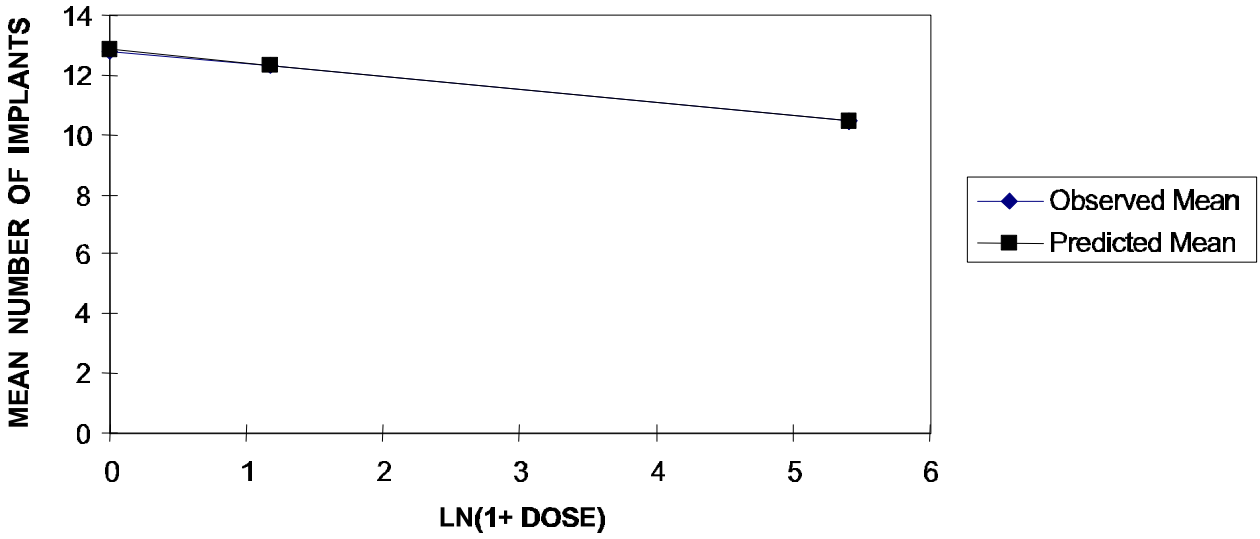


Figure 9-11. Observed versus predicted proportion of live implants (prenatal) using log-linear model.

Figure 9-12. Observed versus predicted mean number of implants (postnatal) using log-linear model.



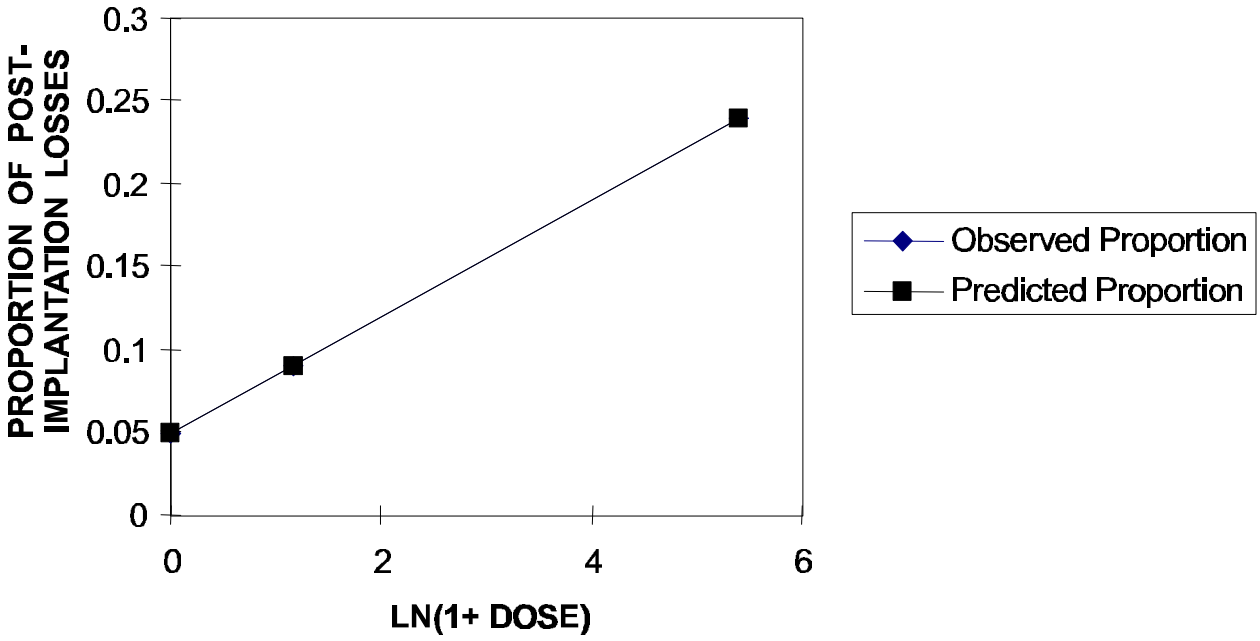
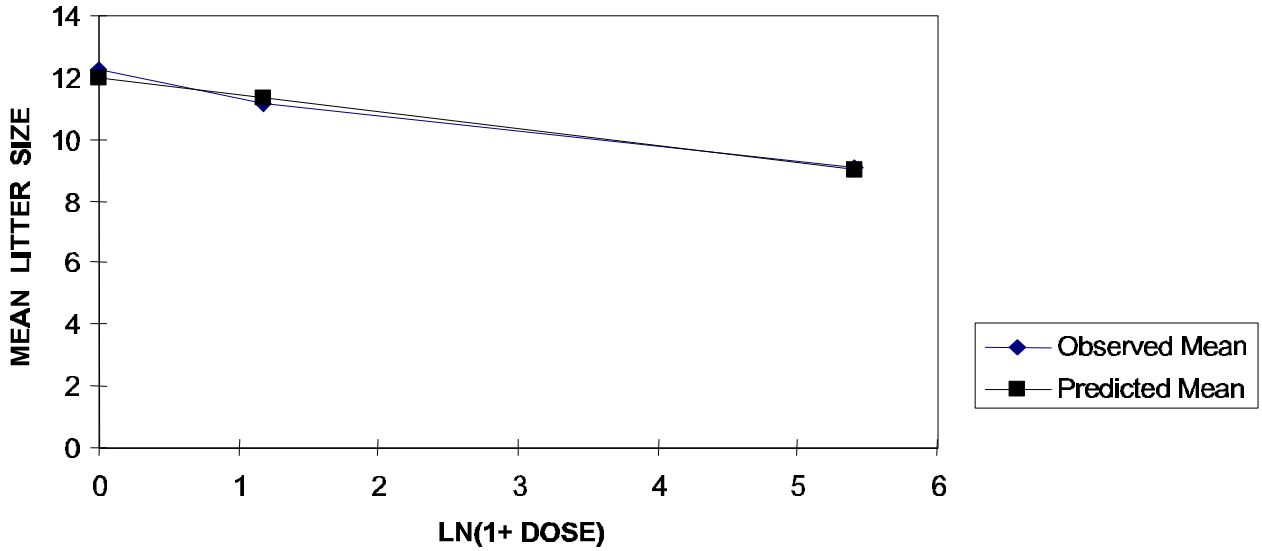


Figure 9-13. Observed versus predicted proportion of post-implantation losses (postnatal) using log-linear model.

Figure 9-14. Observed versus predicted mean litter size at birth using log-linear model.



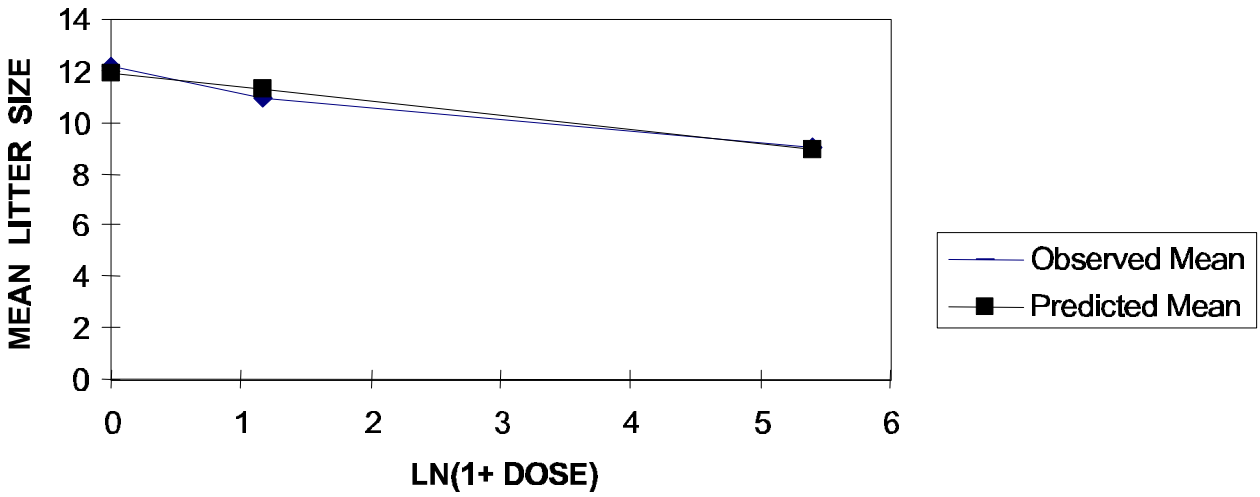


Figure 9-15. Observed versus predicted mean litter size at weaning using log-linear model.

groups, no other endpoints showed a statistically significant increase at 12.5 ppm by pairwise comparison. However, there was a trend toward an increase in the incidence of early and late fetal deaths and percent postimplantation loss, and a decrease in percent live implants and litter size at birth and at weaning in the 12.5 ppm exposure group. Given the overall effect seen on development in this study, the NOAEL for most endpoints was considered to be much closer to 12.5 ppm than to 1,250 ppm. Since litter size at birth and at weaning showed the lowest ECs and LECs, these endpoints will be used for calculation of an RfC.

9.3.4. Ovarian, Uterine, and Testicular Atrophy Modeling

The quantal Wiebull model was used initially to model all data. In cases where this model did not provide a good fit of the data, a log-logistic model was used. The 15-month and chronic ovarian atrophy data could not be fit adequately using the quantal Weibull model. A log-logistic model similar to that used for fetal weight (setting θ_2S and θ_2S to zero) was found to fit the data well. The model was run to determine the probability of additional risk and extra risk. Goodness of fit was determined by a χ^2 test. The model was considered to give a good fit if the p value was greater than 0.05 and a graphical display of the data showed a good fit of the model.

An attempt was made to model various levels of severity in the lesions seen, based on the data shown in Table 9-15. The data for moderate lesions were fit using the quantal Weibull model (Allen et al., 1994b) for dichotomous data. This model can be expressed as:

$$P(d) = 1 - \exp[-(\alpha + \beta d^{\gamma})],$$

where P(d) is the probability of response at exposure level d and α, β, and γ are parameters that are estimated from the observed dose-response data. Parameter constraints were $\alpha \geq 0$; $\beta \geq 0$; $\gamma > 0$. The model was run to determine the probability of additional risk. Goodness of fit was determined by a χ^2 test. The model was considered to provide an acceptable fit if the p value was greater than 0.05 and a graphical display of the data showed a good fit of the model.

Table 9-18 gives the results of fitting the log-logistic model to the 2-year ovarian atrophy data for exposure groups 1-5 and 1-4. The model gave a poor fit for all six exposure groups, because of leveling off of the response at exposures above 62.5 ppm (36 ppm adjusted for continuous exposure). The best fit of the model was for exposure groups 1-4, although the model also fit exposure groups 1-5 well (Figure 9-16; exposures adjusted for continuous exposure), and the EC_{10}s and LEC_{10}s obtained for groups 1-4 and 1-5 were similar. As expected, LEC_{10}s were
lowest for ovarian atrophy at 2 years. Moderate ovarian atrophy at 2 years also was modeled using the quantal Weibull model with exposure groups 1-5 or 1-4. The EC_{10} and LEC_{10} were higher than those for all lesions. Ovarian atrophy data for all six exposure groups at 9 and 15 months were fit using the quantal Weibull or log-logistic model.

Table 9-18. ECs and LECs for ovarian, uterine, and testicular atrophy using the quantal Weibull and log-logistic models [a]

Endpoint	Model	NOAEL/LOAEL	EC_{10}	LEC_{10}	p-Value
Ovarian atrophy - 2 years	Log-logistic (1-5)[b]	1.1 ppm (LOAEL)	0.32	0.22	0.11
			0.29[c]	0.21[c]	
	Log-logistic (1-4)		0.27	0.18	0.96
			0.24[c]	0.17[c]	
Ovarian atrophy - 2 year Moderate lesions only	Quantal Weibull (1-5)	1.1 ppm	3.02	2.35	0.55
	Quantal Weibull (1-4)		2.31	1.67	0.96
Ovarian atrophy - 15 mos	Log-logistic (1-6)	1.1 ppm	2.10	0.72	0.66
Ovarian atrophy - 9 mos	Quantal Weibull (1-6)	11 ppm	20.04	9.95	0.83
Uterine atrophy	Quantal Weibull (1-6)	11 ppm	29.37	18.43	0.66
Testicular atrophy	Quantal Weibull (1-6)	36 ppm	40.59	25.64	0.55

[a]Exposures were adjusted for continuous exposure (e.g., $6.25 \left(\frac{6}{24}\right)\left(\frac{5}{7}\right) = 1.1$ ppm)
[b]Exposure levels included in the model.
[c]Extra risk. All other values are estimates of additional risk.

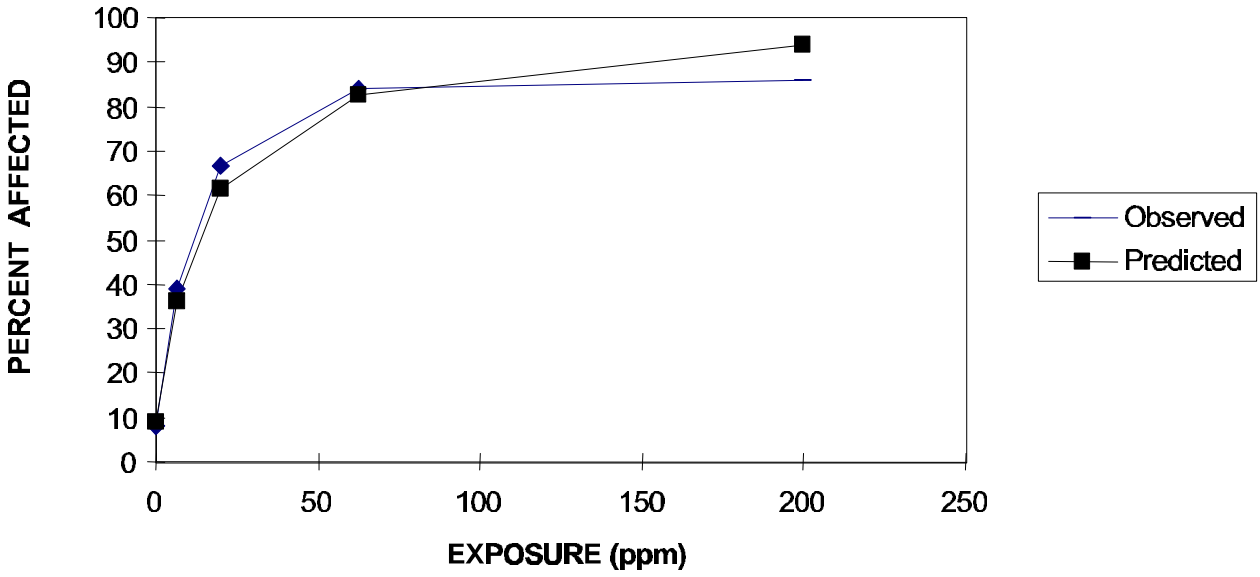


Figure 9-16. Ovarian atrophy (groups 1-5) using log-logistic model.

Uterine and testicular atrophy data also were modeled using the quantal Weibull model. The quantal Weibull model resulted in an acceptable fit of the 2-year uterine atrophy and testicular atrophy data (Table 9-18 and Figures 9-17 and 9-18; exposures adjusted for continuous exposure). However, the EC_{10}s and LEC_{10}s were much higher for these endpoints than for 9-month, 15-month or 2-year ovarian atrophy data. LEC_{10}s were estimated because it has been shown (Allen et al., 1994b) that, for quantal responses, the LEC_{10} is near or below the range of detectable responses. Also, the Proposed Guidelines for Carcinogen Risk Assessment (EPA, 1996) propose use of an LED_{10} as the default point of departure for low-dose extrapolation, and use of an LEC_{10} as a default for noncancer estimation of an RfC would be consistent with this approach.

Although some 9- and 12-month interim sacrifice data were available for ovarian, uterine, and testicular atrophy (Table 9-15), these were less than ideal for modeling because smaller numbers of animals were killed and not all dose groups were represented. In addition, some animals died or became moribund and were killed before the 2-year death time point. To account for the variability in time of death, time-to-response analyses were done using the multistage Weibull model as discussed in Section 9.2.2.2. Exposures were adjusted to the equivalent

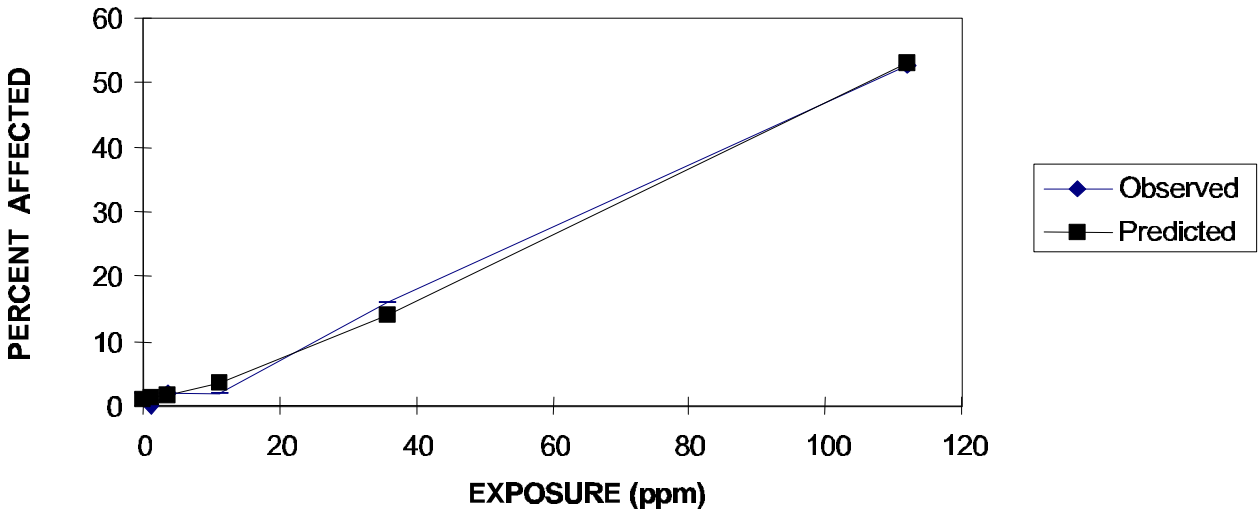
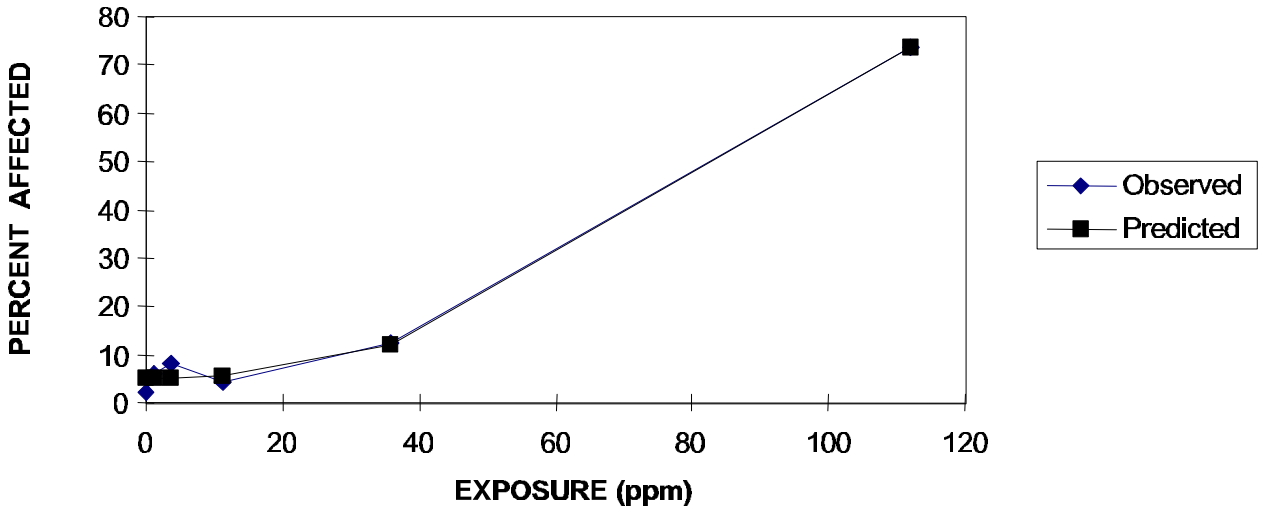


Figure 9-17. Uterine atrophy (groups 1-6) using quantal Weibull model.

Figure 9-18. Testicular atrophy (groups 1-6) using quantal Weibull model .



continuous lifetime exposures. An EC_{10} and an LEC_{10} were calculated in each case. All the reproductive responses were treated as incidental, not fatal. Parameter estimates for each reproductive endpoint are presented in Table 9-19.

Results of the Weibull time-to-response model are shown in Table 9-20. The ECs and LECs were similar to those from other models used for ovarian atrophy, uterine atrophy, and testicular atrophy, with the exception of those from the modeling of testicular atrophy including the highest exposure group, for which the Weibull time-to-response model yields results roughly five times lower than the quantal Weibull model. The quantal Weibull model results for uterine and testicular atrophy were for additional risk, while the Weibull time-to-response results were for extra risk; however, because of the low background rates of both uterine and testicular atrophy, additional risk and extra risk should be nearly the same. The results of the time-to-response model are used in the calculation of an RfC.

The time-to-response model also allows for the calculation of risks at ages less than full lifetime. Thus, if one is concerned about ovarian or uterine atrophy primarily during a woman's reproductive years, one can calculate corresponding EC_{10}s and LEC_{10}s. Assuming reproductive capabilities until 45 years of age yields EC_{10} = 1.3 ppm and LEC_{10} = 1.1 ppm for ovarian atrophy (625 ppm dose group excluded) and EC_{10} = 31 ppm and LEC_{10} = 22 ppm for uterine atrophy (625 ppm group included).

Table 9-19. Parameters for Weibull time-to-response model used to model reproductive effects observed in mice based on ppm butadiene exposure [1]

Response	625 ppm group included	Q0	Q1	Q2	Z
Ovarian atrophy	no	4.86×10^{-6}	7.06×10^{-6}	-	2.21
	yes	9.01×10^{-7}	1.32×10^{-6}	-	2.58
Uterine atrophy	no	6.73×10^{-5}	5.28×10^{-5}	-	1.0
	yes	9.08×10^{-5}	9.74×10^{-6}	1.31×10^{-6}	1.0
Testicular atrophy	no	4.28×10^{-4}	2.24×10^{-5}	-	1.0
	yes	1.60×10^{-4}	1.52×10^{-4}	-	1.0

[1]Each response was considered to be incidental with induction time, T0=0. See Section 9.2.2.2 on time-to-tumor modeling of the mouse carcinogenicity data for a discussion of the Weibull model structure and selection.

Table 9-20. Human benchmark 1,3-butadiene exposure concentrations calculated for reproductive effects observed in mice using a Weibull time-to-response model (extra risk)

Response	625 ppm group included	Based on ppm butadiene exposure	
		EC_{10}	LEC_{10}
Ovarian atrophy	no	0.497	0.382
	yes	0.473	0.369
Uterine atrophy	no	18.8	12.0
	yes	24.0	15.6
Testicular atrophy	no	44.3	15.9
	yes	6.54	5.39

9.3.5. Summary and Conclusions

ECs and LECs were estimated for three types of exposure scenarios to 1,3-butadiene based on different endpoints:

1. Short-term exposure (10 days)**C**fetal weight reduction
2. Subchronic exposure (10 weeks)**C**male-mediated developmental toxicity
3. Chronic exposure**C**ovarian, uterine and testicular atrophy

These analyses demonstrate approaches for estimation of ECs and LECs based on continuous and quantal data.

Results of the fetal weight analysis illustrate how both continuous and quantal modeling approaches can be used for continuous data. All of the LECs calculated were below the LOAEL of 40 ppm, except for two LECs calculated using the continuous power model, which were near this value. Since the hybrid modeling approach is considered the preferred method for modeling continuous data, the LEC_{10} of 13.7 ppm from this model will be used for calculating the reference concentration for developmental toxicity for short-term exposure (RfC_{DT}).

Results of the analysis for male-mediated developmental toxicity following 10 weeks of exposure gave ECs and LECs much lower than those from the 10-day exposures based on fetal weight. Therefore, the LEC_{10} for the dominant lethal study will be used to calculate an RfC for a subchronic exposure scenario.

Modeling of the 2-year ovarian atrophy data, the effect occurring at the lowest chronic exposure level, gave a good fit with the log-logistic model, but only when the highest exposure level was dropped. This approach was justified because the responses leveled off for the top three exposure groups. The LECs derived for a 10% increase in additional risk or extra risk were 5- to 6-fold below the LOAEL of 6.25 ppm. When the time-to-response model was applied to account for interim sacrifice data and early mortality, an LEC_{10} of 0.38 ppm (extra risk) was calculated, a value similar to that using the log-logistic model.

Ovarian atrophy has been shown to be related to the amount of the diepoxide metabolite in the tissue (Doerr et al., 1996). Uterine atrophy may be secondary to ovarian atrophy, and thus may also be related to the amount of diepoxide metabolite formation. Modeling of the ovarian atrophy and uterine atrophy data was considered based on internal dose of the diepoxide metabolite. However, an adequate pharmacokinetic model was not available to estimate levels of the diepoxide metabolite (Chapter 8).

RfC calculations will be made for both ovarian atrophy, the reproductive effect occurring at the lowest chronic exposure level, and testicular atrophy, the reproductive effect observed in male mice following chronic exposure.

9.4. REFERENCE CONCENTRATIONS FOR REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

9.4.1. Introduction

As discussed in Chapter 5 and Section 9.3, a variety of reproductive and developmental effects have been observed in mice and rats exposed to 1,3-butadiene by inhalation. (There are no human reproductive or developmental data available for 1,3-butadiene.) In this section, sample reference concentrations (RfCs) are calculated for the most sensitive reproductive and developmental endpoints, i.e., those effects exhibiting responses at the lowest exposure concentrations from various exposure scenarios, using both the traditional NOAEL/LOAEL approach and the "benchmark dose" approach (Crump, 1984). A reference concentration (or dose) is an estimate of a daily exposure to humans that is "likely to be without an appreciable risk of deleterious [noncancer] effects during a lifetime" (Barnes et al., 1988). The final reported RfC will be based on the endpoint resulting in the lowest calculated RfC level. This RfC will be solely an RfC for reproductive and developmental effects (R/D RfC) and not a true RfC because other noncancer endpoints were not considered.

9.4.2. Calculation of RfCs

The most sensitive developmental effect was decreased fetal weight in the mouse. The most sensitive reproductive effects observed in subchronic exposure studies were decreased litter size at birth and at weaning in dominant lethal studies of mice (i.e., male mice are exposed to 1,3-butadiene and effects on litters are measured after mating to unexposed females). These effects are highly correlated and both yielded the same modeled effective dose results (Table 9-17). Litter size at birth reflects both decreased implants and increased fetal deaths, while litter size at weaning also reflects neonatal deaths. Dominant lethal effects in humans would likely be manifested as spontaneous abortions, miscarriages, stillbirths, or very early deaths. From chronic exposure studies (2-year bioassays), the most sensitive reproductive endpoints were ovarian atrophy in female mice and testicular atrophy in male mice.

Table 9-21 summarizes the EC_{10} (i.e., the exposure concentration resulting in a 10% increase in risk based on modeling the exposure-response data in the observable range), the LEC_{10} (i.e., the 95% lower confidence limit on the exposure concentration estimated to result in a 10% increase in risk), and the NOAEL (i.e., no observed adverse effect level) or LOAEL (i.e., lowest observed adverse effect level; reported when no NOAEL was observed) for these 1,3-butadiene-induced effects. Table 9-21 also provides sample calculations of RfCs using the NOAEL (or LOAEL) as well as the LEC_{10} as "points of departure." Uncertainty factors are then applied to the "point of departure" to calculate the RfC.

Typically, a factor of 10 is used for interspecies uncertainty when the "point of departure" is based on nonhuman data; however, when ppm equivalence across species is assumed as was done here, a factor of 3 is used instead. Thus, in Table 9-21, an interspecies uncertainty factor of 3 was used for all endpoints except ovarian atrophy. For ovarian atrophy, there is convincing evidence that the diepoxide metabolite (1,2:3,4-diepoxybutane, DEB) is required to elicit the effect and, while the differences cannot be quantified without an adequate physiologically based pharmacokinetic (PBPK) model, it is expected that humans produce lower concentrations of DEB than mice, based on differences in metabolic rates. Thus, an uncertainty factor of 1.5 was used for ovarian

atrophy to account for differences between mice and humans in the amount of DEB produced, yet allow that humans may be more sensitive to DEB.

A large degree of human variability has been observed in metabolic activities that could affect 1,3-butadiene toxicity. For example, Seaton et al. (1995) measured a 60-fold variation in the initial rate of oxidation of 1,2-epoxy-3-butene (EB) to DEB in microsomes from 10 different human livers. However, overall variability in total metabolism and susceptibility is unknown, thus the conventional intraspecies uncertainty factor of 10 for human variability was used for each endpoint in Table 9-21.

With respect to the acute/subchronic-to-chronic uncertainty factor, none was needed for ovarian or testicular atrophy because these effects were based on chronic studies. No acute-to-chronic uncertainty factor was used for fetal weight either, because only exposures during

Table 9-21. Points of departure and RfC calculations for reproductive and developmental effects of 1,3-butadiene

Effect	NOAEL (or LOAEL) (ppm)	EC_{10} (ppm)	LEC_{10} (ppm)	Interspecies uncertainty factor	Intraspecies uncertainty factor	Acute/ subchronic-to-chronic uncertainty factor	LOAEL-to-NOAEL uncertainty factor	Risk reduction factor [a]	RfC based on NOAEL (ppm)	RfC based on LEC_{10} (ppm)
Decreased fetal weight		28	14	3	10	1[b]		3		0.14
	40 (LOAEL) (10 d, 6h/d, GD 6-15)			3	10	1[b]	10		0.13	
Decreased litter size at birth (or at weaning) (dominant lethal effect)		0.20[c]	0.15[c]	3	10	3		3		0.0005
	2.2 (LOAEL) (10 week, adjusted to 24 h/d)			3	10	3	10		0.002	
Ovarian atrophy		0.50[d]	0.38[d]	1.5[e]	10	1		3		0.008
	1.1 (LOAEL) (2 year, adjusted to 24 h/d)			1.5[e]	10	1	10		0.007	
Testicular atrophy		6.5[d]	5.4[d]	3	10	1		3		0.05
	36 (2 year, adjusted to 24 h/d)			3	10	1	1		1.2	

[a]To decrease risk to below what would be a detectable level, analogous to the LOAEL-to-NOAEL uncertainty factor.
[b]Although from acute study, only exposure during gestation is assumed to be relevant to fetal weight.
cAdjusted to 24-h daily exposure.
[d]Adjusted to chronic continuous exposure.
[e]There is strong evidence that ovarian atrophy is caused specifically by the metabolite 1,2:3,4-diepoxybutane, and humans are thought to produce less of this metabolite than mice, although their relative sensitivity to the metabolite is unknown (see text).

gestation are relevant. Although dominant lethal effects appear to occur with exposure during a specific time period of spermatogenesis (i.e., only certain stages of developing sperm appear susceptible), chronic exposure might result in continuous induction of these effects, so a factor of 3 was used.

Under the NOAEL/LOAEL approach, the NOAEL is defined as the exposure level for which there is no observed adverse effect, although it is circumscribed by the detection limit of the study. For endpoints for which there is no NOAEL, an uncertainty factor of 10 is typically used to attempt to extrapolate from the LOAEL to a level at which there are presumed to be no detectable effects. In the benchmark dose approach, the typical "point of departure" corresponds to a 10% increased response level, which is explicitly not a no-effect level. In this risk assessment, a risk reduction factor of 3 was used to extrapolate to a level below which no detectable effects would be expected, analogous to the LOAEL-to-NOAEL uncertainty factor. Final guidance on this methodology is still being developed by EPA.

In addition to the sample RfCs presented in Table 9-21 for lifetime 1,3-butadiene exposure, two RfCs were calculated for subchronic exposure. An RfC_{DT} of 0.14 ppm for developmental toxicity from short-term exposures was calculated for decreased fetal weight, using the same factors depicted in Table 9-21. This RfC_{DT} is identical to the sample RfC calculated for decreased fetal weight because no subchronic-to-chronic uncertainty factor was used in that calculation. Finally, an RfC for subchronic exposure was calculated for the decreased litter size endpoints from the subchronic dominant lethal study. Using the LEC_{10} of 0.15 ppm and uncertainty factors of 3 for interspecies extrapolation, 10 for intraspecies variability, and 3 for risk reduction (analogous to the LOAEL-to-NOAEL uncertainty factor), as described above, yields an R/D RfC for subchronic exposure of 0.0015 ppm.

9.4.3. Discussion

The EC_{10}s in Table 9-21 suggest that the dominant lethal (male-mediated) effect is the most sensitive reproductive/developmental endpoint (i.e., the "critical" endpoint), and thus should be the basis for the final R/D RfC. The dominant lethal effect also yields the lowest sample RfC of 0.5 ppb. To arrive at the final R/D RfC, a further uncertainty factor of 3 is used to account for the lack of comprehensive reproductive testing, especially the absence of a multigenerational study. This final calculation yields an R/D RfC of 0.15 ppb.

There are substantial uncertainties in estimating low-exposure human risks for reproductive and developmental effects observed in animals exposed to high concentrations of an agent. It is generally believed that there is a nonlinear low-dose exposure-response relationship for noncancer effects, and perhaps a threshold, although this is difficult to demonstrate empirically. The shape of this low-dose exposure-response relationship is unclear,

however, so RfCs are calculated for noncancer effects rather than exposure-based risk estimates. The major uncertainties considered in deriving an RfC include the extrapolation of effects observed in animals to humans (interspecies extrapolation), the potential existence of sensitive human subpopulations resulting from human (intraspecies) variability, and various deficiencies in the database. These areas of uncertainty are addressed to some extent by the uncertainty factors. Other methodological uncertainties arise in the determination of the "point of departure" and in the selection of the relevant exposure metric for equating animal exposure-response relationships to humans.

There are a number of limitations in using the NOAEL/LOAEL approach for obtaining a "point of departure"; these have inspired the development of an alternative "benchmark dose" (or concentration) methodology. First, the NOAEL/LOAEL approach relies on one exposure level and ignores the rest of the exposure-response data. Second, the NOAEL/LOAELs depend explicitly on the specific exposure levels selected for the study. They are also a function of study power because a LOAEL is the lowest exposure level with a statistically significant increase in an adverse effect, whereas a NOAEL could represent an increase that failed to attain statistical significance. Finally, NOAEL/LOAELs are not readily comparable across endpoints or studies because they can refer to different response levels.

The alternative benchmark concentration approach involves modeling the full exposure-response curve in the observable range and calculating an effective concentration (EC) corresponding to some level of response (e.g., 10%) that can be used as a point of comparison across endpoints and studies (the 10% effect level is typically at the low end of the observable range, although sometimes a lower level of response can be estimated). The LEC_{10} is being considered as the default "point of departure" to take into account statistical variability around the EC_{10} estimate. While the benchmark concentration approach alleviates some of the limitations of the NOAEL/LOAEL approach, there are still uncertainties regarding the appropriate exposure-response model to use. It is generally expected that models that provide a good fit to the data in the observable range should yield reasonably similar EC_{10}s, as shown for quantal models by Allen et al. (1994b).

As shown in Table 9-21, these two approaches yielded nearly identical RfCs for decreased fetal weight and for ovarian atrophy. For the dominant lethal effect of decreased litter size, the RfCs were similar, with that from the NOAEL/LOAEL approach four-fold higher than that from the benchmark concentration approach. For testicular atrophy, on the other hand, the NOAEL-based RfC is over 20 times higher than the LEC_{10}-based RfC. At least part of this discrepancy is likely attributable to the fact that the time-to-response modeling conducted to derive the LEC_{10} took into account the decreased survival times in the higher exposure groups in the chronic study. This had the effect of increasing the effective percent affected in the

midrange of the exposure-response curve, which otherwise is fairly flat. This assessment advances the use of the benchmark dose/concentration approach.

Uncertainties also exist in the choice of exposure metric. Ideally, NOAEL or LOAELs and LEC_{10}s (or EC_{10}s) should be converted to appropriate human equivalent exposures before using these exposure levels as "points of departure." Theoretically, this is best accomplished by using a PBPK model to convert animal exposures to biologically effective doses to the target organ and then to convert these tissue concentrations back to human exposures to the parent compound. Unfortunately, the current PBPK data and models are inadequate for use in risk assessment; therefore, exposure concentrations of 1,3-butadiene are used as the default exposure metric (this risk assessment assumes equivalence of effects from equivalent ppm exposures across species). For the lifetime chronic exposure study, demonstrating ovarian and testicular atrophy, mouse exposure concentrations were adjusted to human equivalent continuous chronic exposures.

For the subchronic and acute studies, however, the appropriate time frame for exposure averaging is unclear. Typically, daily exposures resulting in nondevelopmental effects have been adjusted to an equivalent 24-h exposure, while exposures resulting in developmental effects have not been adjusted (U.S. EPA IRIS online database, 1997). Consistent with this approach, 1,3-butadiene exposures resulting in dominant lethal effects have been adjusted to a 24-h exposure, whereas exposure levels from fetal weight studies have not been adjusted. The exposure concentrations for these subchronic and acute effects have not been adjusted to reflect total duration of exposure because the critical time frames are unknown. Thus, for example, a 1-day exposure is treated equivalently to a 10-week exposure to the same daily level. Also, for developmental effects, a 4-h exposure to 50 ppm would be treated equivalently to an 8-h exposure to 50 ppm.

Finally, there are uncertainties in the uncertainty factors used to derive the RfC from the "point of departure." These factors are largely arbitrary. In particular, the shape of the exposure-response curve below the observable range is unknown, and it is uncertain that the NOAEL or the LOAEL/10 or the $LEC_{10}/3$ actually represent no-effect levels, independent of the application of the interspecies and intraspecies uncertainty factors.

9.4.4. Conclusions

In conclusion, an R/D RfC of 0.15 ppb was calculated for the critical endpoint of the dominant lethal effect of decreased litter size at birth (or at weaning), based on mouse data. This reference concentration, the uncertainties discussed above notwithstanding, is presumed to represent a daily exposure to humans that is likely to be without an appreciable risk of reproductive or developmental effects during a lifetime.

In addition, an RfC_{DT} of 0.14 ppm for developmental toxicity from short-term exposures was calculated based on fetal weight data for mice, and an R/D RfC for subchronic exposure of 0.0015 ppm was obtained based on the dominant lethal results in mice. Each of these RfCs was calculated using benchmark concentration methodology.

9.5. CONCLUSIONS ON QUANTITATIVE RISK ESTIMATES

In this chapter, a lifetime extra unit cancer risk (MLE) of 9×10^{-3} per ppm of continuous 1,3-butadiene exposure was calculated based on linear modeling and extrapolation of the excess leukemia mortality reported in a high-quality occupational epidemiology study. Using this cancer potency estimate, the chronic exposure level resulting in an increased cancer risk of 10^{-6} can be estimated as follows: $(10^{-6})/(9 \times 10^{-3}/\text{ppm}) = 1 \times 10^{-4}$ ppm = 0.1 ppb. The 95% UCL on the unit cancer risk was 2×10^{-2} per ppm.

A range of human cancer potency estimates from 4×10^{-3}/ppm to 0.29/ppm was also calculated based on a variety of tumors observed in mice and rats exposed to 1,3-butadiene. These risk estimates are considered inferior to those based on the epidemiological data, primarily because of the large uncertainties in extrapolating 1,3-butadiene cancer risks across species in light of the large unexplained differences in responses of rats and mice.

In addition, benchmark doses and reference concentrations were calculated for an assortment of reproductive and developmental effects observed in mice exposed to 1,3-butadiene. An R/D RfC of 0.15 ppb was obtained for the critical effect of decreased litter size at birth (or at weaning) observed in dominant lethal studies of mice, using a benchmark concentration approach to obtain the "point of departure." This R/D RfC is presumed to be a chronic exposure level without "appreciable risk" of reproductive or developmental effects. Although other noncancer effects were not examined, the reproductive endpoints were quite sensitive, and it is likely that the R/D RfC is protective against other noncancer effects as well.

Finally, an RfC_{DT} of 0.1 ppm for developmental toxicity from short-term exposures was calculated from mouse fetal weight data, and an R/D RfC for subchronic exposures of 0.0015 ppm was derived from the dominant lethal results in mice, each using benchmark concentration methodology.